Breast Cancer Risk From Low-Dose Exposures to Ionizing Radiation: Results of Parallel Analysis of Three Exposed Populations of Women [1]

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ABSTRACT—Breast cancer incidence data were analyzed from three populations of women exposed to ionizing radiation: survivors of the Hiroshima and Nagasaki atomic bombs, patients in Massachusetts tuberculosis sanitoria who were exposed to multiple chest fluoroscopies, and patients treated by X-rays for acute postpartum mastitis in Rochester, New York. Parallel analyses by radiation dose, age at exposure, and time after exposure suggested that risk of radiation-induced cancer increased approximately linearly with increasing dose and was heavily dependent on age at exposure; however, the risk was otherwise remarkably similar among the three populations, at least for ages 10-40 years at exposure, and followed the same temporal pattern of occurrence as did breast cancer incidence in nonexposed women of similar ages.—JNCI 65: 353-376, 1980.

Public concern about breast cancer risk from exposures to low doses of ionizing radiation (*1*) and the continuing, unresolved scientific debate about the magnitude of the risks (2) emphasize the many existing uncertainties about the relationship between radiation dose and cancer risk. One may easily overlook the fact that more information is available on the carcinogenic effects of ionizing radiation than on any other important environmental carcinogen. With the recent publication of five major studies of breast cancer incidence in populations of irradiated women (3-7), there has been a remarkable accumulation of information about female breast cancer. Radiation-induced breast cancer has occurred among women with histories of X-ray therapy for acute postpartum mastitis (*4*, 8), women who received multiple chest fluoroscopies during pneumothorax treatment for TB (5, 9), and female survivors of the Hiroshima and Nagasaki A-bomb explosions (3, 7). In addition, risks of radiation-induced breast cancer have been established (although less securely) among women given X-ray therapy for other benign breast diseases (6). Moreover, the risk estimates associated with these observations reveal that the female breast is unusually sensitive to radiation carcinogenesis (*10*).

Still uncertain are the precise levels of risks associated with various dose levels (especially the low-dose levels characteristic of mammography); the shape of the dose-response curve; the effects of dose fractionation, protraction, and radiation quality (LET); the influence of age and other characteristics of the subject at the time of exposure; and the temporal distribution of risk following exposure. The results of various individual studies are highly informative with respect to many of these questions, but intriguing inconsistencies also exist. For example, the overall estimates of risk per rad from two recent studies of A-bomb survivors (*3-7*) are considerably lower than those from three recent studies of medically exposed populations (*4-6*). Also, two of the medical series suggest a dependence of latency period on dose (*4*, 6), whereas the fluoroscope series and the two A-bomb survivor series do not (3, 5, 7, *11*, *12*). For one to suggest reasons for these and other differences is easy (e.g., by ascribing them to differences in susceptibility between Japanese and Western women, to age differences among the irradiated populations, or to confounding between dose and age), but without new data analyses these suggestions remain mere speculations. By extensive reanalyses of the original data from several large studies, the present paper differs from earlier reviews of published works linking breast cancer risk and radiation exposure. Whereas many of the conclusions reached are expected to be identical to those reached in earlier reviews or original studies, the empirical bases for such conclusions should be clearer.

Besides availability of the original data, certain requirements must be met for a meaningful parallel reanalysis of data from several studies by use of identical methods and assumptions. There must be sufficient years of follow-up and numbers of subjects and high enough dose levels so that statistically stable risk estimates can be obtained even after subdivision of the data by age and other factors. For contrast in terms of dose there must be a valid comparison group or a broad range of radiation dose and, preferably, in-

ABBREVIATIONS USED: **ATB = at time of bombing; df = degrees of freedom; LET = linear energy transfer; LSS = life-span study; RBE = relative biologic effectiveness; RERF = Radiation Effects Research Foundation; TB = tuberculosis; WY= woman-years.**

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dividual measurement of dose for each study. These requirements are best satisfied by the 1950-74 LSS sample incidence study by Tokunaga et al. (7), the Massachusetts TB-fluoroscopy study by Boice and Monson (5), and the recent analysis of the Rochester, New York, mastitis series, with nonexposed mastitis and sibling controls reported by Shore et al. (4).

MATERIALS AND METHODS

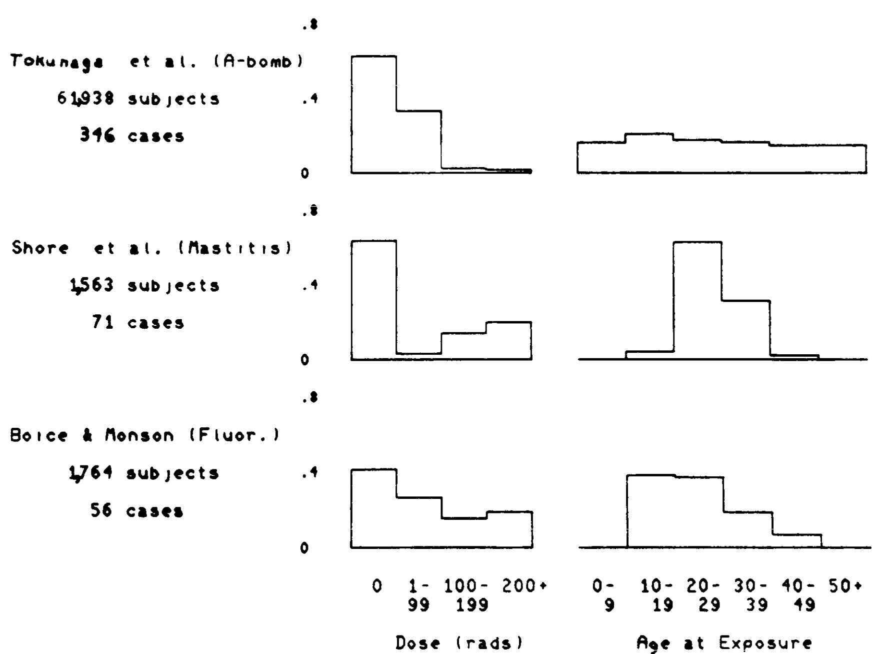
Basic data, including numbers of cases and WY of observation for risk, are given in Appendix table 1-3 by age at exposure (or age at beginning of exposure), by radiation dose interval, by calendar time after exposure (excluding the first 5 yr), and by city for A-bomb survivors. Such detail is necessary to account for differences among the three studies that may be artifactually related to the risk estimates given in the original papers. Except for certain comparisons requiring tabulation of data by both age at exposure and age at risk, the analyses described in this paper can be reconstructed with the use of the data in Appendix table 1-3.

Differences in age and dose distribution among the three studies are summarized in text-figure 1. The selected nature of the two medical series and the unselected nature of the LSS series are reflected in the age distributions. The dose distributions illustrate the substantially greater number of A-bomb survivors exposed at low doses. At high-dose levels the three series are based on similar numbers.

Certain differences exist among the three populations represented in Appendix tables 1-3 that were not addressable by analytic methods. The LSS series was ascertained by examinations of death certificates, clinical records, and pathologic materials from hospitals, university medical schools, and tumor and tissue registries in Hiroshima and Nagasaki. Whereas the death certificate data were complete, migration of survivors, especially the younger ones, from the two cities since 1950 (the date of the census on which the LSS sample was based) was likely to have caused overall underascertainment of incidence (3). Migration was not different among dose categories (*13*) nor did evidence exist of ascertainment bias with respect to dose (3). The most probable effect of the migration is a slight downward bias in estimated risk.

A more speculative consideration is that TB in young patients who were frequently fluoroscoped may have been associated with underweight. Age at menarche is related both to fatness (*14*) and to breast cancer risk in later life (15). TB patients therefore conceivably could be a low-risk group, although no decreased risk was apparent among the nonexposed patients (5). However, whereas the experience of the 3 comparison groups (nonirradiated mastitis patients and sisters of irradiated and nonirradiated patients) for the mastitis series effectively minimizes the possibility that the observed radiation dose response was an artifact of the treated condition (4), the response to radiation of lactating or inflamed tissue might differ from that of other breast tissue.

Dose estimates were more reliable for patients given radiation therapy than for patients given multiple fluoroscopic examinations or for A-bomb survivors. Dose estimation for both pneumothorax patients and A-bomb survivors had to be based on reconstructions of their exposures (16, *17*). Jablon (*18*) estimated the standard errors of individual estimates for the LSS sample to be ±30%. He suggested that the higher dose estimates probably tended to be biased upward, whereas the lower estimates were probably biased downward.



TEXT-FIGURE 1.—Distribution of subjects by study, radiation dose, and age at exposure. Fluor. = fluoroscopy.

WY at that dose (usually the number of WY corresponding to a dose interval with average dose D) divided by the current value of the fitted function at dose D; i.e., the rate times the WY is assumed to correspond approximately to a Poisson variate with mean equal to the incidence predicted by the product of the fitted function times the WY at risk. In practice, χ^2 values for lack of fit seemed somewhat smaller than would be expected on the basis of random variation, given a true dose-response model. This observation suggested that the true variances may be slightly smaller than the assumed values. However, no reason was found to believe that the weights are incorrect for curve fitting.

RESULTS AND DISCUSSION

RBE of Neutrons

The large size of the LSS sample and its relative strength at low- and intermediate-dose levels make it the most suitable basis for inferences about the shape of the dose-response curve. Whereas the breast tissue of Japanese and American women may respond differently to radiation, the assumption will be made that these differences might involve the magnitude of the response but not the shape or functional form of the dose-response curve. A major objection to this assumption is the difference in the types of radiation received by the exposed women in the two U.S. medical series and by the Japanese A-bomb survivors. Although almost all of the radiation received by the Nagasaki survivors was in the form of gamma rays, comparable to the X-rays received by the U.S. women, the radiation from the Hiroshima bomb contained a neutron component amounting to 13-30% of the total absorbed dose in breast tissue. Because experiments in animals have suggested different dose-response curves for gamma- and neutron-induced tumors (24-28), evaluation of any differences in dose response between the two cities is important.

This question was addressed by fitting to the dose-specific breast cancer rates for Hiroshima and Nagasaki, standardized to the age distribution of the combined cities (table 1), a function linear-quadratic in gamma dose ($D\gamma$) and linear in neutron dose (D_n), denoted *LQ-L* for brevity:

$$I(D\gamma, D_n) = \alpha_0 + \alpha_1 D\gamma + \alpha_2 D\gamma^2 + \beta_1 D_n.$$

In this function all parameters are constrained to be nonnegative, and the intercept α_0 is allowed to be different for the two cities. Radiobiologically, no dose-squared term in D_n is needed because closely spaced ionizing events are the rule; i.e., the probability of two events in a given locus is approximately the same as that of a single event. The additional complexity of cell killing was not introduced because it would have added too many parameters. However, no evidence was found of a highdose reduction in slope consistent with cell killing.

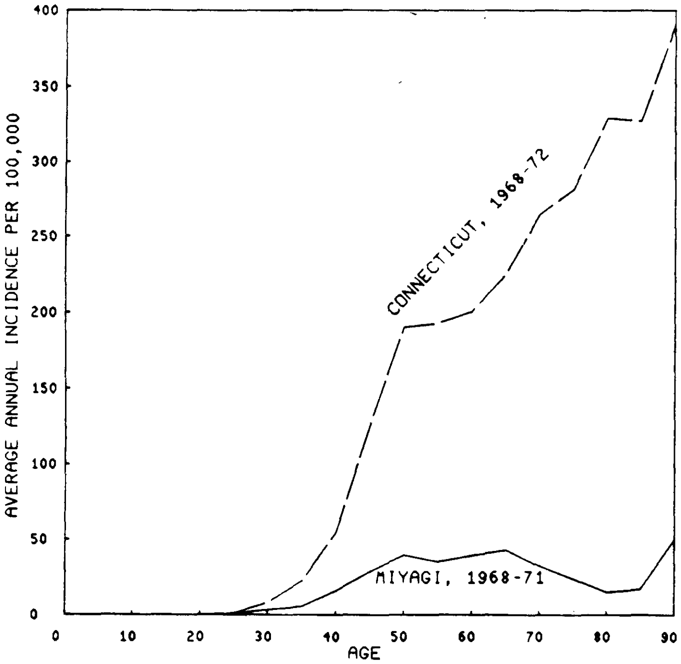
TABLE 1.—*Summary data for regression analyses of breast cancer incidence among A-bomb survivors, 1950–74*

City	Dose interval, rads	WY at risk	Average dose, rads		Age-adjusted rate/ 100,000 WY
			Gamma	Neutron	
Hiroshima	0	680,372	0	0	24.2
	1–3	82,913	1.5	0.2	27.2
	4–9	63,099	5.4	0.8	25.2
	10–19	75,610	11.1	1.7	22.5
	20–49	55,856	27.3	4.3	35.3
	50–99	30,240	59.3	9.9	37.7
	100–199	17,057	118.5	21.5	79.9
	200–299	6,913	202.9	41.6	34.9
	300–399	3,212	277.9	63.2	74.3
	≥400	2,690	450.5	128.2	203.8
Nagasaki	0	149,365	0	0	17.0
	1–3	40,933	1.9	0	18.7
	4–9	38,769	5.6	0	17.5
	10–19	26,578	13.0	0	16.5
	20–49	18,288	33.5	0.1	31.0
	50–99	15,962	70.6	0.2	20.9
	100–199	17,883	142.1	0.9	54.3
	200–299	5,844	238.2	2.3	106.8
	300–399	2,456	339.7	4.0	45.3
	≥400	2,394	578.4	7.2	111.3

We obtained identical fitted curves by using the above function and a restricted form in which the parameter α_2 was assumed to be zero (denoted *L-L*) (table 2). The estimated ratio of the linear coefficients for neutron and gamma dose was 1.42± 1.86 under the *L-L* model. Thus the linear model RBE for neutrons was estimated to be close to 1, and with 95% confidence to be less than 4.48. The data do not suggest a purely quadratic dose response for gamma rays; restricting the linear coefficient α_1 in $I(D\gamma, D_n)$ to zero (the Q-L model) yielded a fitted curve with a significantly poorer fit to the data than did the *LQ-L* model ($P=$ 0.003). This result is in marked contrast to the results of similar curve-fitting analyses of leukemia incidence data, in which the *Q-L* model appears to fit the data as well as does the *L-L* model (29, 30).

The *L*, *Q* and *LQ* functions of rem dose equivalents were fitted separately to Hiroshima and Nagasaki rates for different RBE assumptions, including constant RBE values of 1, 1.42, and 5 and the variable RBE corresponding to the *Q-L* analysis in table 2, RBE = $40.7/D_n^{½}$ (table 3). In all cases for which the RBE was assumed to be constant, the *L* and *LQ* models yielded closely similar fitted functions that agreed significantly better with the data than did the fitted function corresponding to the Q model. Even for the variable RBE assumption, under which risk should be proportional to the square of rem dose, the fit of the Q model was only marginally better than that of the *L* model, worse than that of the *LQ* model in the case of Hiroshima, and significantly worse than the fit of the *L* and *LQ* models for Nagasaki.

For constant RBE values of 1 and 1.42 very little difference was found between the two cities with



TEXT-FIGURE 2.—Comparison of age-specific breast cancer rates in the United States (Connecticut Tumor Registry) and Japan (Miyagi and Okayama Prefecture Tumor Registries).

The most obvious difference among the three studies is the great difference in natural age-specific breast cancer incidence in Japan and the United States (text-fig. 2) (19). The data in Appendix tables 1-3, therefore, provided the basis for a test of whether the effect of radiation on breast cancer incidence was influenced by natural cancer rates.

The dependence of breast cancer risk on radiation dose has been shown to vary by age at exposure (3, 5, 7). The age-specific data were generally too sparse, however, for fitting any but the simplest dose-response functions. As a way around this dilemma, we assumed that within a given population, the shape (but not necessarily the magnitude) of the dose-response function for breast cancer was independent of age at exposure. Given this assumption, the shape of the dose-response curve for each population should be obtainable from an investigation of summary rates, standardized for age at exposure to adjust for possible confounding of age with radiation dose.

The functional forms fitted to the dose-response data from the three main studies considered in this report are special cases of the general form:

$$I(D)=(\alpha_0+\alpha_1 D+\alpha_2 D^2)\exp(-\beta_1 D-\beta_2 D^2),$$

where $I(D)$ is the incidence of breast cancer at dose D (radiation dose in rads) and where the parameters α_0, α_1, α_2, β_1, and β_2 are constrained to be nonnegative. This functional form, discussed by Brown (20) and Upton (21), can be viewed as basically a linear function (with α_0 and α_1 being essentially the only parameters relevant to risk at very low dose levels) with modifications that allowed the fitted curve to express upward curvature at low-dose levels (α_2) and downward curvature at high-dose levels (β_1 and β_2). The constraint that all parameters be nonnegative has its basis in radiobiologic theory. The linear coefficient α_1 represented that part of the carcinogenesis response that was proportional to dose, i.e., the probability of a single ionizing event at a given locus in a cell nucleus. For low-LET radiation such as gamma ray or X-ray, ionizing events were sparsely distributed along a radiation track, and the probability of two closely spaced events was proportional to the square of dose. The quadratic coefficient α_2 represented the additional effect of two closely spaced events as compared to a single ionization, and this additional effect cannot be negative. The coefficients β_1 and β_2 were similarly defined, but with respect to the competing effect of cell killing, which removed cells that might otherwise be involved in carcinogenesis.

Because a statistical trade-off existed between the number of parameters fitted and the accuracy of the parameter estimates (with the assumption that the model was true), parameters α_2, β_1, and β_2 were retained in the model only if their inclusion significantly improved the fit of the model to the data. In fact, we found that nothing was gained and considerable precision was lost by the inclusion of both β_1 and β_2 in the above form. Of the two, β_1 accounted for less variation and so was dropped.

For simplification of references to the various versions of $I(D)$ in the text, they are denoted as follows:

$$I(D)=\alpha_0+\alpha_1 D, \qquad [L]$$

$$I(D)=\alpha_0+\alpha_1 D+\alpha_2 D^2, \qquad [LQ]$$

$$I(D)=(\alpha_0+\alpha_1 D)\exp(-\beta_2 D^2), \qquad [L\text{-}K]$$

$$I(D)=(\alpha_0+\alpha_1 D+\alpha_2 D^2)\exp(-\beta_2 D^2); \qquad [LQ\text{-}K]$$

that is, *L* is the linear form, *LQ* the linear-quadratic form with upward curvature, *L-K* the form with downward curvature, and *LQ-K the* most general form, with upward curvature at low-dose levels and downward curvature at high-dose levels.

We also considered pure quadratic variants of *L Q* *(Q)* and *LQ-K* (Q-K) above, i.e., functions in which the linear term was assumed to be zero:

$$I(D)=\alpha_0+\alpha_2 D^2, \qquad [Q]$$

$$I(D)=(\alpha_0+\alpha_2 D^2)\exp(-\beta_2 D^2). \qquad [Q\text{-}K]$$

These functional forms were, however, thought to be inappropriate for estimation of low-dose risk: Although the models with linear terms might yield small low-dose risk estimates, this must necessarily occur when the linear coefficient is assumed to be zero. They were included mainly for completeness, as a check on the adequacy of the other forms.

The curve-fitting method, for which technical details can be found in (22, 23), is an iterative weighted least-squares procedure. On any given iteration, the weight corresponding to the observed rate (simple or age-standardized) at dose *D* is assumed to be the number of

TABLE 2.—*Summary of regression analyses of age-adjusted breast cancers rates for Hiroshima and Nagasaki, with respect to gamma and neutron dose*

α_1[a,b]	α_2[a,b]	β_1[a,b]	RBE[a]	χ^2, df	*P*-value
Linear-quadratic gamma, linear neutron model: Excess risk $=\alpha_1 D\gamma+\alpha_2 D\gamma^2+\beta_1 D_n$					
2.18±0.76	0[c]	3.10±3.68	≤1.42±1.97	8.4, 15	0.91
Linear model: Excess risk $=\alpha_1 D\gamma+\beta_1 D_n$					
2.18±0.50	—	3.10±3.56	1.42±1.86	8.4, 16	0.94
Square gamma, linear neutron model: Excess risk $=\alpha_2 D\gamma^2+\beta_1 D_n$					
—	0.0515±0.0214	8.54±4.57	$(40.7\pm16.9)/\sqrt{D_n}$	17.0, 16	0.39

[a] Estimate ± SD.
[b] All regression coefficients are scaled by a factor of 10^6.
[c] The best-fitting parameter value would be negative; the value of zero results from the prior constraint that the parameter be nonnegative. Constraints are not accounted for in computation of error estimates for the parameter estimates. Therefore, error estimates may be misleading if, as in this case, there are active constraints on any of the parameters of the fitted function. For the data considered in this paper, however, the error estimates for the remaining parameters appear to be little affected by the presence of an active constraint; similar error estimates were obtained when the active constraints were removed.

respect to fitted functions corresponding to the *L*, Q and ***LQ*** models, whereas for RBE values of 5 and $40.7/D_n^{1/2}$ the fitted functions tended to differ. Also, little difference existed between the fitted curves for RBE = 1 and RBE = 1.42, the value obtained from the ***L-L*** model analysis in table 2. Dose-response curves and fitted linear regressions for the RBE value of 1 are shown by city in text-figure 3.

Whereas the above analysis cannot be said to resolve the question of the RBE of neutrons with respect to breast cancer in women, little evidence exists to indicate that the breast cancer responses to exposure to

TABLE 3.—*Regression analyses of age-adjusted rates with respect to dose-equivalent values in rem for various neutron-RBE assumptions; LSS data, 1950–74, by city*

Dose-response model[a]	Coefficient	Hiroshima			Nagasaki		
		Estimate ± SD[b]	χ^2, df	*P*-value	Estimate ± SD[b]	χ^2, df	*P*-value
RBE = 1: $D=D\gamma+D_n$							
L	α_1	2.34±0.51	5.1, 8	0.75	2.20±0.42	3.3, 8	0.91
Q	α_2	0.064±0.026	12.5, 8	0.12	0.062±0.024	9.4, 8	0.31
LQ	α_1	2.26±0.95			2.20±0.82		
	α_2	0.003±0.029	5.1, 7	0.65	0[c]	3.3, 7	0.86
RBE = 1.42: $D=D\gamma+1.42\ D_n$							
L	α_1	2.18±0.48	5.1, 8	0.75	2.19±0.42	3.3, 8	0.91
Q	α_2	0.054±0.023	12.8, 8	0.12	0.062±0.023	9.5, 8	0.30
LQ	α_1	2.13±0.89			2.19±0.82		
	α_2	0.002±0.024	5.2, 7	0.64	0[c]	3.3, 7	0.86
RBE = 5: $D=D\gamma+5D_n$							
L	α_1	1.38±0.31	5.2, 8	0.74	2.12±0.41	3.3, 8	0.91
Q	α_2	0.019±0.009	14.3, 8	0.07	0.057±0.022	9.7, 8	0.29
LQ	α_1	1.38±0.56			2.12±0.80		
	α_2	0[c]	5.2, 7	0.64	0[c]	3.3, 7	0.86
RBE $=40.7/D_n^{1/2}$: $D=(D\gamma^2+(40.7)^2 D_n)^{1/2}$							
L	α_1	1.38±0.37	7.7, 8	0.46	2.15±0.41	3.2, 8	0.92
Q	α_2	0.047±0.013	7.2, 8	0.52	0.061±0.023	9.1, 8	0.33
LQ	α_1	0.70±0.58			2.15±0.81		
	α_2	0.026±0.020	5.6, 7	0.59	0[c]	3.2, 7	0.87

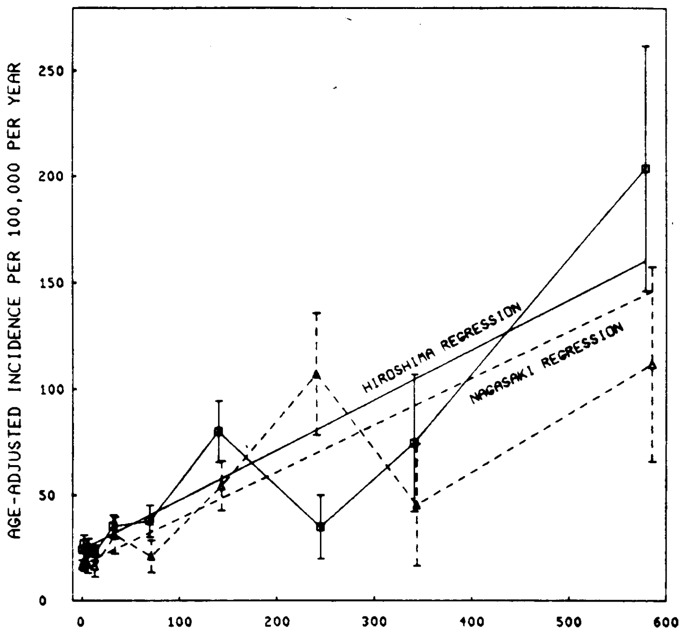
[a] Models and their equations are as follows:

L incidence $=\alpha_0+\alpha_1 D$;

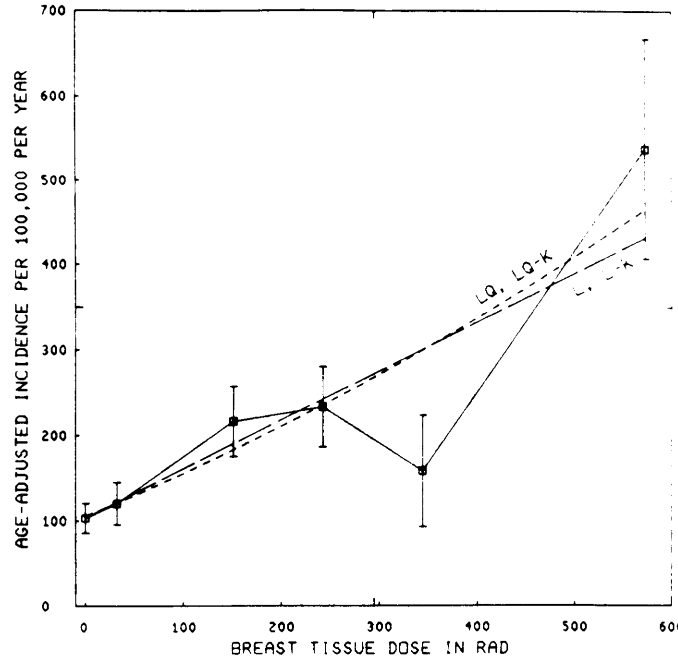
Q incidence $=\alpha_0+\alpha_2 D^2$;

LQ incidence $=\alpha_0+\alpha_1 D+\alpha_2 D^2$.

[b] *See* footnote *b*, table 2.
[c] *See* footnote *c*, table 2.



TEXT-FIGURE 3.—A-bomb survivors, 1950-74: Dose-specific breast cancer rates (with 50% confidence limits) and fitted linear regressions on dose by city of exposure.

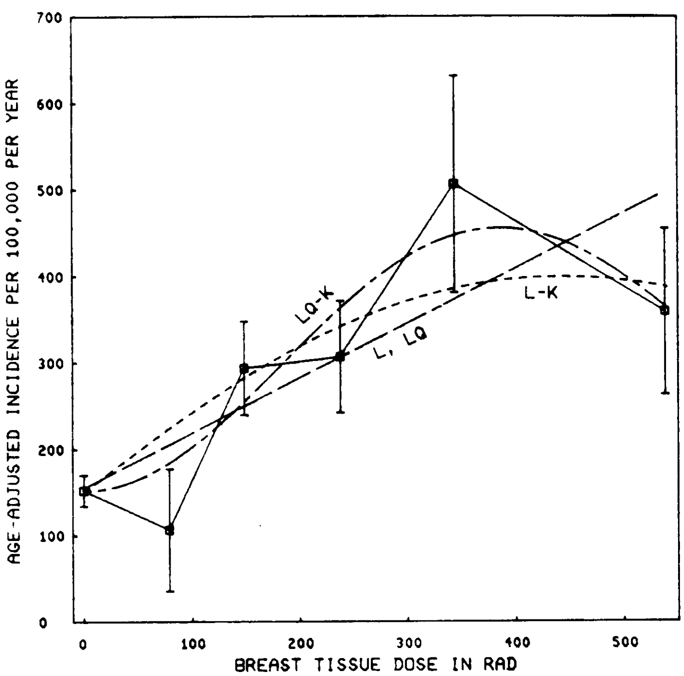


TEXT-FIGURE 5.—Massachusetts fluoroscopy series: Dose-specific breast cancer rates (with 50% confidence limits) and fitted dose-response functions.

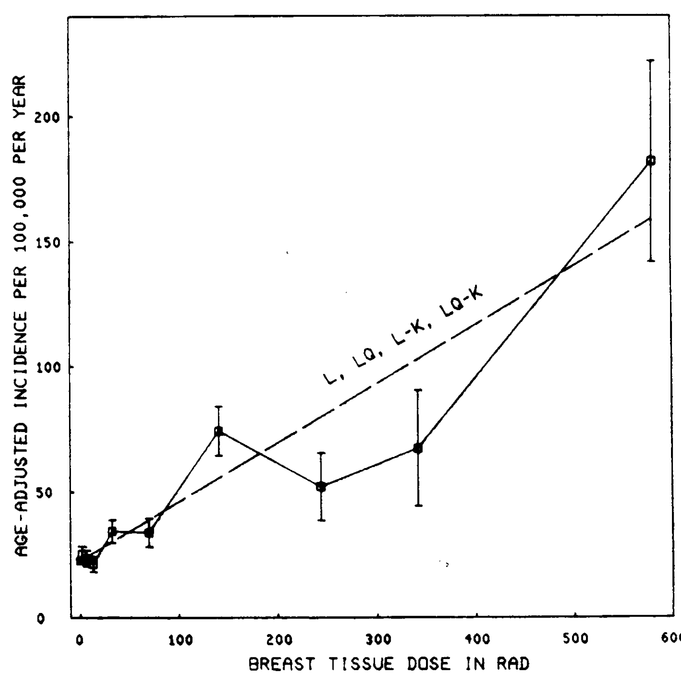
gamma and neutron radiations were different. Accordingly, a simple pooling of the Hiroshima and Nagasaki data under the assumption of equivalence in carcinogenic effectiveness between neutron and gamma radiation exposures to the breast introduced no apparent bias.

Dose Response

In the analyses described below it was assumed that whereas the overall level of the breast cancer response to irradiation may depend on age at exposure, so that care must be taken to avoid confounding of dose and



TEXT-FIGURE 4.—Rochester mastitis series: Dose-specific rates (with 50% confidence limits) and fitted dose-response functions. Dose is average to both breasts.



TEXT-FIGURE 6.—Japanese A-bomb survivors, 1950-74: Dose-specific breast cancer rates (with 50% confidence limits) standardized for city, and fitted dose-response functions.

age, the shape of the dose-response function does not depend on age. This assumption allowed the data to be pooled by standardizing dose-specific incidence rates according to a standard age distribution. For each series, the overall age distribution for that series was used as a standard. The standardized rates were fitted, by an iterative weighted least squares algorithm, to each of the four main functional forms described under "Materials and Methods": a linearly increasing function of dose (L), a linear-quadratic function with upward curvature (LQ), a linear function modified to allow for negative curvature at high doses (L-K), and a linear-quadratic function with the same modification (LQ-K). In addition, we used functional forms Q and Q-K, also described above, that lacked linear terms in dose.

Text-figures 4-6 and tables 4-6 show the fitted curves and parameter values corresponding to the functional forms L, LQ, L-K, and LQ-K, when fitted to the age-standardized data of Appendix tables 1-3. Parametric constraints reduced L-K to L and LQ-K to LQ for the Massachusetts fluoroscopy data; LQ to L for the New York mastitis series; and LQ, L-K, and LQ-K to L for the LSS series. Although the improvement of fit of L Q over L for the Massachusetts series was negligible ($P=0.32$ for α_2), that of L-K over L for the New York series reached suggestive levels of significance ($P=0.10$ for β_1), whereas LQ-K was not a noticeable improvement over L-K ($P=0.30$ for α_2). Of the four main functional forms considered, therefore, only the linear form L could be fitted to the numerically strongest data set, but some support was given to the existence of high-dose downward curvature by the New York mastitis data.

A stronger result was obtained with single-breast data from the mastitis series (table 7, text-fig. 7). For these data the downward-curving form L-K gave an improved fit over the linear form L ($P=0.02$), which suggested that cell killing at high-dose levels (400-1,400 rads) may be a factor of some importance for unfractionated and relatively unfractionated exposures. Neither the Massachusetts fluoroscopy study (5), the earlier Nova Scotia series (9), nor the LSS study (7) suggests dose-response relationships in which breast cancer

TABLE 4A.—*Rochester mastitis series: Curve-fitting analyses of age-adjusted dose-response data*

Data	Dose range in rads					
	0	40–99	100–199	200–299	300–399	≥400
Mean dose, rads	0	79	148	237	343	538
No. of cancer patients	32	1	13	9	6	6
No. of WY	20,650	951	4,478	3,273	1,400	1,734
Rate[a]	15.3	10.3	29.3	27.8	45.6	34.5

[a] Breast cancers/10,000 WY at risk, adjusted to the distribution by age of WY for all doses for this series.

TABLE 4B.—*Results of curve-fitting analyses of data from the Rochester mastitis series*

Model[a]	Parameter	Estimate ± SD[b]	Test for lack of fit	
			χ^2, df	P-value
L	α_1	5.6±1.5	2.0, 4	0.74
LQ	α_1	5.6±4.3		
	α_2	0[c]	2.0, 3	0.57
L-K	α_1	8.6±2.9		
	β_2	1.8±1.4	1.2, 3	0.75
LQ-K	α_1	3.2±11.4		
	α_2	0.037±0.069		
	β_2	4.8±4.0	1.1, 2	0.58
Q	α_2	0.011±0.060	5.0, 4	0.29
Q-K	α_2	0.055±0.017		
	β_2	5.6±1.5	1.2, 3	0.75

[a] Models and regression equations are as follows:

L: $I(D)=\alpha_0+\alpha_1 D$;

LQ: $I(D)=\alpha_0+\alpha_1 D+\alpha_2 D^2$;

L-K: $I(D)=(\alpha_0+\alpha_1 D)\exp(-\beta_2 D^2)$;

LQ-K: $I(D)=(\alpha_0+\alpha_1 D+\alpha_2 D^2)\exp(-\beta_2 D^2)$;

Q: $I(D)=\alpha_0+\alpha_2 D^2$; and

Q-K: $I(D)=(\alpha_0+\alpha_2 D^2)\exp(-\beta_2 D^2)$.

[b] *See* footnote *b*, table 2.

[c] *See* footnote *c*, table 2.

TABLE 5A.—*Massachusetts fluoroscopy series: Curve-fitting analyses of age-adjusted dose-response data*

Data	Dose range in rads					
	0	1–99	100–199	200–299	300–399	≥400
Mean dose, rads	0	32	151	242	344	573
No. of cancer patients	14	10	12	11	3	4
No. of WY	15,691	8,869	5,862	4,710	1,697	1,429
Rate[a]	10.1	11.9	20.7	23.3	15.5	52.7

[a] Breast cancers/10,000 WY at risk, adjusted to the distribution by age of WY for all doses for this series.

TABLE 5B.—*Results of curve-fitting analyses of data from the Massachusetts fluoroscopy series*

Model[a]	Parameter	Estimate ± SD[b]	Test for lack of fit	
			χ^2, df	P-value
L	α_1	5.6±1.2	1.6, 4	0.81
LQ	α_1	4.5±3.0		
	α_2	0.0029±0.0076	1.5, 3	0.68
L-K	α_1	5.6±2.3		
	β_2	0[c]	1.6, 3	0.66
LQ-K	α_1	4.5±8.6		
	α_2	0.0029±0.057		
	β_2	0[c]	1.5, 2	0.47
Q	α_2	0.013±0.004	3.0, 4	0.56
Q-K	α_2	0.022±0.014		
	β_2	1.6±2.2	2.5, 3	0.48

[a] *See* footnote *a*, table 4B.

[b] *See* footnote *b*, table 2.

[c] *See* footnote *c*, table 2.

TABLE 6A.—*Japanese A-bomb survivor series: Curve-fitting analyses of age-adjusted dose-response data*

Data	Dose range in rads									
	0	1–3	4–9	10–19	20–49	50–99	100–199	200–299	300–399	≥400
Mean dose, rads	0	1.8	6.1	12.9	32.1	69.6	141	244	342	580
No. of cancer patients	191	30	22	22	25	16	24	8	4	9
No. of WY	829,737	123,846	101,868	102,189	74,144	46,202	34,940	12,757	5,668	5,084
Rate[a]	2.25	2.52	2.33	2.11	3.42	3.37	7.38	5.20	6.74	18.17

[a] Breast cancers/10,000 WY at risk, adjusted to the distribution by age of WY, for all doses, for this series. Rate was also adjusted for city.

TABLE 6B.—*Results of curve-fitting analyses of data from the Japanese A-bomb survivor series*

Model[a]	Parameter	Estimate ± SD[b]	Test for lack of fit: χ^2, df	Test for lack of fit: *P*-value
L	α_1	2.3±0.4	6.0, 8	0.65
LQ	α_1	2.3±0.8		
	α_2	0[c]	6.0, 7	0.54
L–K	α_1	2.3±0.6		
	β_2	0[c]	6.0, 7	0.54
LQ–K	α_1	2.3±1.5		
	α_2	0[c]		
	β_2	0[c]	6.0, 6	0.42
Q	α_2	0.0065±0.0024	19.2, 8	0.014
Q–K	α_2	0.015±0.006		
	β_2	3.7±2.0	11.8, 7	0.11

[a] *See* footnote *a*, table 4B.
[b] *See* footnote *b*, table 2.
[c] *See* footnote *c*, table 2.

incidence decreases at high-dose levels. The Massachusetts patients received cumulative doses to the breasts as high as 1,000 rads, and some of the Nova Scotia patients received doses as high as several thousand rads. The highly fractionated nature of the fluoroscopy exposures possibly could explain the absence of a high-dose downturn in observed incidence in these studies, if indeed the mastitis curve truly reflects the underlying dose-response relationship. The LSS dose-response curve, however, cannot be said to reflect any fractionation of dose. Nevertheless, the fact remains that one of the three data sets considered in detail here suggests the existence of downward curvature of the dose-response curve at high-dose levels.

Tables 4–6 also give the results of regressions with models Q and ***Q-K***, in which the linear coefficients in models ***LQ*** and ***LQ-K***, respectively, were assumed to be zero. These models did not fit the age-standardized data as well as did the corresponding models with linear terms. The data set strongest at the low end of the dose scale, the LSS series, gave the least support to these models, whereas the mastitis series, which is weak at doses between 0 and 100 rads, discriminated only poorly between models ***L-K*** and Q-K. Overall, the analysis provides empirical support, as far as breast cancer is concerned, for the presumptive position that low-dose risk estimates should not be based on dose-response models lacking a linear term.

Age at Exposure

Case reports of breast cancers occurring in young women with histories of high-dose radiation therapy to the chest during infancy have been interpreted as examples of radiogenic cancer because of the high

TABLE 7A.—*Rochester mastitis series: Curve-fitting analyses of dose-response data for single breasts, 5–34 years after entry into study*

Data[a]	Dose range in rads					
	0	60–199	200–299	300–399	400–599	600–1,400
Mean dose in rads	0	150	249	349	467	800
No. of cancer patients by age AE, yr: 15–19	0	0	2	0	0	0
20–29	15	1	5	6	4	1
30–39	17	1	3	5	3	1
40–44	3	0	1	0	0	0
Total	35	2	11	11	7	2
No. of BY[b] by age AE, yr: 15–19	1,804	78	266	122	211	37
20–29	30,766	1,670	2,754	2,210	2,656	1,222
30–39	16,007	545	1,215	779	1,197	458
40–44	951	70	25	114	109	26
Total	49,528	2,363	4,260	3,225	4,173	1,743
Age-adjusted rate[c]	7.0	9.5	30.0	37.0	17.3	11.9

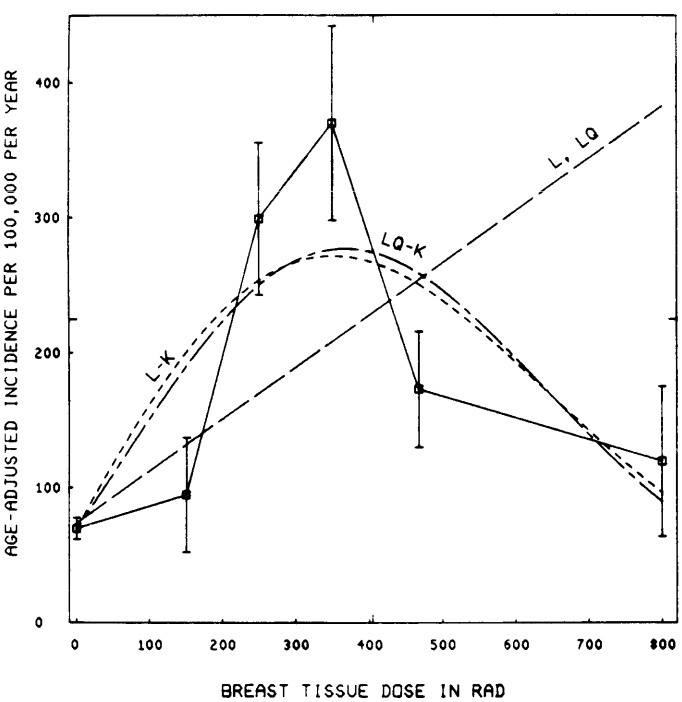
[a] AE = at exposure.
[b] Breast yr (BY) at observation for risk.
[c] Breast cancers/10,000 BY at risk.

TABLE 7B.—*Results of curve-fitting analyses for single-breast data*

Model[a]	Parameter	Estimate ± SD[b]	Test for lack of fit: χ^2, df	Test for lack of fit: *P*-value
L	α_1	3.9±1.8	12.8, 4	0.012
LQ	α_1	3.9±5.4		
	α_2	0[c]	12.8, 3	0.005
L–K	α_1	9.8±3.7		
	β_2	3.4±1.6	3.9, 3	0.27
LQ–K	α_1	7.8±14.8		
	α_2	0.010±0.066		
	β_2	4.2±4.9	3.9, 2	0.14
Q	α_2	0.0055±0.0049	27.2, 4	0.00002
Q–K	α_2	0.049±0.021		
	β_2	6.6±2.4	4.1, 3	0.25

[a] *See* footnote *a*, table 4B.
[b] *See* footnote *b*, table 2.
[c] *See* footnote *c*, table 2.

of radiation exposure involved and because cancer is so rare in young women (32, 32). Substantial evidence from controlled studies of increased breast cancer risk in women exposed to ionizing radiation before the age of 10 years is lacking, however. Only 1 (nonexposed) breast cancer was found among women O-9 years old ATB in the 1950-69 LSS series (3). Five cancers in women of the same age group were found in the 1950-74 series, including 1 with a breast tissue dose of 57 rads and 4 with less than 10 rads (7). However, this cohort is only now reaching the ages at which the radiation-related excess in the cohort of women 10-19 years old ATB became apparent (3).



TEXT-FIGURE 7.—Rochester mastitis series: Breast cancer rates per breast (with 50% confidence limits) and fitted dose-response functions.

Another 5–10 years of follow-up should determine the extent to which radiation exposure has affected breast cancer incidence in the youngest cohort.

Relative risks for 100 or more rads versus 0 rad by age at exposure are given in table 8 for the LSS, the Massachusetts fluoroscopy study, and the New York mastitis series. For women exposed between 10 and 39 years of age, the relative risks for the three series are mutually supportive in that each strengthens the evidence for a radiation dose effect on breast cancer incidence in women exposed at these ages. The picture is less clear, however, for women older at the time of exposure. The Rochester mastitis data suggest a high relative risk for women 40-44 years of age at time of exposure, but the numbers are small (3 cases among 14 irradiated patients). The Massachusetts fluoroscopy data for women 40-49 years of age at first exposure are especially weak, inasmuch as there were only 58 exposed women and the case numbers in each exposure group are less than expected according to population rates. Neither medical series contains any information about risk for women exposed at older ages.

The real problem, however, is that the numerically strong LSS data are contradictory. The high but statistically nonsignificant relative risk for women 50 years or older ATB is based on relatively small numbers. However, a statistically significant relative risk was observed in the 1950-69 LSS series, from virtually the same information, in which the high-dose interval was defined in terms of kerma rather than dose to breast tissue (≥ 100 rads kerma = ≥75 rads dose to breast) and therefore included 1 more case. Against this must be set the unexpected absence of any dose effect in the cohort of women 40-49 years old ATB. This anomaly, which also occurred in the 1950-69 LSS series but was not detected in the analysis because different age intervals ATB (20-34 and 35-49 yr of age) were used (3), occurred in both cities.

The deficit among A-bomb survivors who were 40-49 years of age ATB could conceivably have been due to the effects of irradiation on the ovaries at ages associ-

TABLE 8.—*Age-specific relative risk (odds ratios), ≥100 rads vs. 0 rad, by series and age at exposure*

Age at exposure, yr	Rochester mastitis patients: Estimate	Rochester mastitis patients: *P*-value	Massachusetts fluoroscopy patients: Estimate	Massachusetts fluoroscopy patients: *P*-value	LSS[a] patients, 1950–74: Estimate	LSS[a] patients, 1950–74: *P*-value
10–19	—	—[b]	4.8	0.003	5.6	<0.0001
20–29	2.2	0.02	1.5	0.27	2.8	0.002
30–39	1.6	0.16	1.4	0.48	4.0	<0.0001
40–49	5.2	—[c]	2.0	—[d]	0.6	0.69
≥50	—	—	—	—	3.1	0.09

[a] Adjusted for between-city differences.
[b] Ages 15–19 yr; 2 high-dose cases vs. 0 control case.
[c] Ages 40–44 yr; 3 high-dose cases vs. 1 control case.
[d] One high-dose case vs. 1 control case.

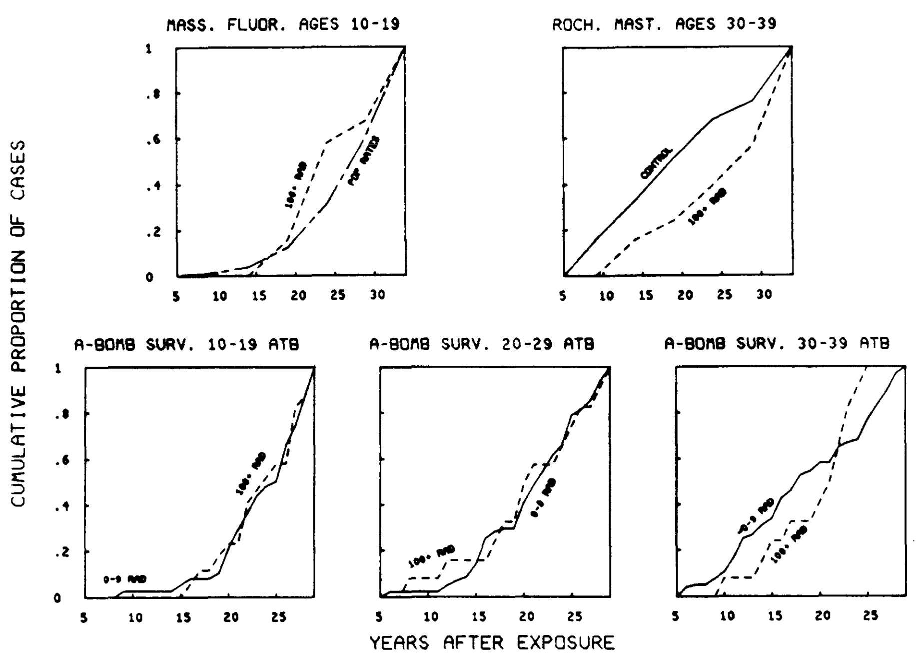
ated with marked changes in ovarian function. Sawada (33) found that among 880 exposed women post menarche and prior to menopause, one-half experienced amenorrhea after the bombings. This condition was particularly marked among women in their forties. Amenorrhea in women of 34 years of age or under was transient in every case, but among those 45-49 years of age it was permanent and continued to menopause in over 80%. Women treated with X-irradiation for metropathia hemorrhagica at Scottish radiotherapy centers between 1940 and 1960 and who were in their 40's when irradiated later had less than one-half the breast cancer mortality expected according to population rates (34). However, no such reduction in breast cancer incidence was found among a somewhat older and much smaller group of women in whom artificial menopause was induced by X-irradiation (35). Doses to ovaries were about one-half as great as doses to breast tissue among A-bomb survivors and amounted to about a 100-rad average dose to ovaries among survivors with 100 rads or more to the breasts (36). Doses were on the order of several hundreds of rads in the two series of women given therapeutic pelvic irradiation. At any rate, the findings for women in the LSS series exposed between the ages of 40 and 49 years considerably complicate the problem of risk estimation for women with breast tissue exposure at these ages.

If doubts about the appropriateness of population controls for the Swedish radiation therapy series (6) could be resolved, the evidence from that study might argue strongly for an increased risk of breast cancer among women exposed to radiation at ages over 40 years. Statistically significant excess incidences, compared with population rates, were found at all ages in women at time of radiation exposure including those 40-49 and 50 years of age or older.

Latency Period

"Latency period" is used here to denote elapsed time between a radiation exposure and the diagnosis of a breast cancer caused by that exposure; i.e., the definition is conditional on a breast cancer having occurred and is therefore different from the definition used in competing risk analysis in which the latency period may extend considerably beyond the normal length of life (37). Although not directly observable, latency period can be studied by comparison of the temporal distribution of breast cancer incidence occurring in a high-dose group having a high and statistically significant relative risk (and therefore, presumably, a high proportion of radiation-caused cancers) and in an appropriate low-dose control group.

Individual diagnosis dates for breast cancer cases are not different, on the average, between high-dose (≥ 100 rads) and low-dose (nonexposed and O-9 rads) groups in the LSS series for any age interval. Distributions with respect to date of diagnosis, in the form of cumulative incidence curves, are compared in text-figure 8 for the LSS cohorts 10-19, 20-29, and 30-39 years of age ATB; for the Massachusetts fluoroscopy patients 10-19 years old at first treatment; and for the Rochester mastitis patients treated at ages 20-29 years. These were the only cohorts in each series satisfying the relative risk and statistical significance requirements mentioned above; for each, the corresponding relative risk estimate in table 8 suggests that over one-



TEXT-FIGURE 8.—Cumulative proportions of breast cancer patients over time since exposure by series and age at exposure for data sets with high relative risks and sufficient No. of cases. MASS. FLUOR. = Massachusetts fluoroscopy; ROCH. MAST. = Rochester mastitis; SURV. = survivor.

half of the high-dose cases were radiation related. Even so, there were only 4 low-dose (nonexposed) breast cancer cases in the cohort of Massachusetts patients exposed at 10-19 years of age, and therefore a curve based on population rates was substituted for the low-dose curve. The curves offer no support to the hypothesis that radiation-induced breast cancers tend to occur earlier than do other breast cancers; in fact, they suggest that although radiation may increase the lifetime risk of breast cancer, its age distribution is unaffected. This conclusion also resulted from earlier and more detailed analyses (presented elsewhere) of data from the 1950-69 and 1950-74 LSS sample series (*11*, 12); the result is in marked contrast to the wavelike temporal pattern observed for radiation-induced leukemia. The present analysis shows that the temporal patterns of breast cancer incidence in the two medical series also are unaffected by dose. The association between dose and latency period reported by Shore et al. (*4*) did not appear in the present analysis in which age at exposure was specifically taken into account. The association reported by Baral et al. (6) may have a similar explanation; in that series dose and age at exposure clearly are correlated.

The existence of a minimal latency period, during which no excess risk occurs, is suggested by consideration of the time required for a tumor to reach a clinically detectable stage. In view of the preceding paragraph, the concept may be relevant only to women already at or near ages of nonnegligible natural breast cancer risk at the time of exposure. Because breast cancer incidence increases with advancing age and because the available evidence for increased risk in women exposed at ages over 40 years is either nonexistent (for the LSS cohort 40-49 yr of age ATB) or based on small numbers (for the LSS cohort ≥50 yr old ATB and, in the two medical series, for women 40-44 yr of age at first exposure), there is probably a built-in bias toward overestimation of the minimal latency period. The Rochester mastitis data show statistically significant high-dose excesses of breast cancer 10-14 years after treatment and, more strongly, 20-24 and 25-29 years after treatment, but a high-dose deficit occurred for the period 15-19 years after treatment. Data from the generally younger Massachusetts fluoroscopy series first show a statistically significant excess 15-19 years after first exposure, which continues during later periods. The age-adjusted relative risk for 5-9 years after exposure is high but not statistically significant for the 1950-74 LSS series; the relative risks remain fairly constant, whereas the P-values decrease rapidly for subsequent 5-year periods ($P=$ 0.051 for 1955-59). However, the 1950-69 LSS data, which for the earliest years of follow-up are essentially the same as those of the most recent series except for different dose cuts, yielded a statistically significant excess (for ≥100 rads kerma) for years 5-9 after 1945. No data are available for the period 1945-49. In view of these results and the above suggestions of possible upward bias, it seems reasonable to assume a minimum latency period of about 5 years for women 25 years old or older at exposure. However, a further period of perhaps 5 years may be required before there is substantial expression of the excess risk.

The existence or nonexistence of a maximum latency period (and therefore a delimited risk "plateau") cannot be determined from the available data, except that if one exists it must be greater than 30 years.

TABLE 9.—*L-model risk estimates by series and age at first exposure*

Series	Age at exposure, yr	Absolute risk/rad,[a] estimate ± SD	Percent increase in relative risk/rad,[b] estimate ± SD
Rochester mastitis patients	15–19	27.9±19.8[c]	—
	20–29	6.3±2.0	0.43±0.18
	30–39	9.4±3.4	0.35±0.16
	40–44	52.1±21.0[c]	1.57±1.21[c]
Massachusetts fluoroscopy patients	10–19	8.9±3.1	0.84±0.45
	20–29	3.8±2.1	0.23±0.16
	30–39	6.9±4.8[c]	2.3±3.1
	40–44	6.4±15.6[c]	0.54±1.7[c]
LSS survivors, 1950–74[d]	10–19	8.9±2.1	3.0±0.97
	20–29	2.9±0.84	0.88±0.29
	30–39	4.7±2.5	1.4±0.85
	40–49	−1.0±0.45	−0.30±0.14
	≥50	3.3±2.2	0.97±0.68

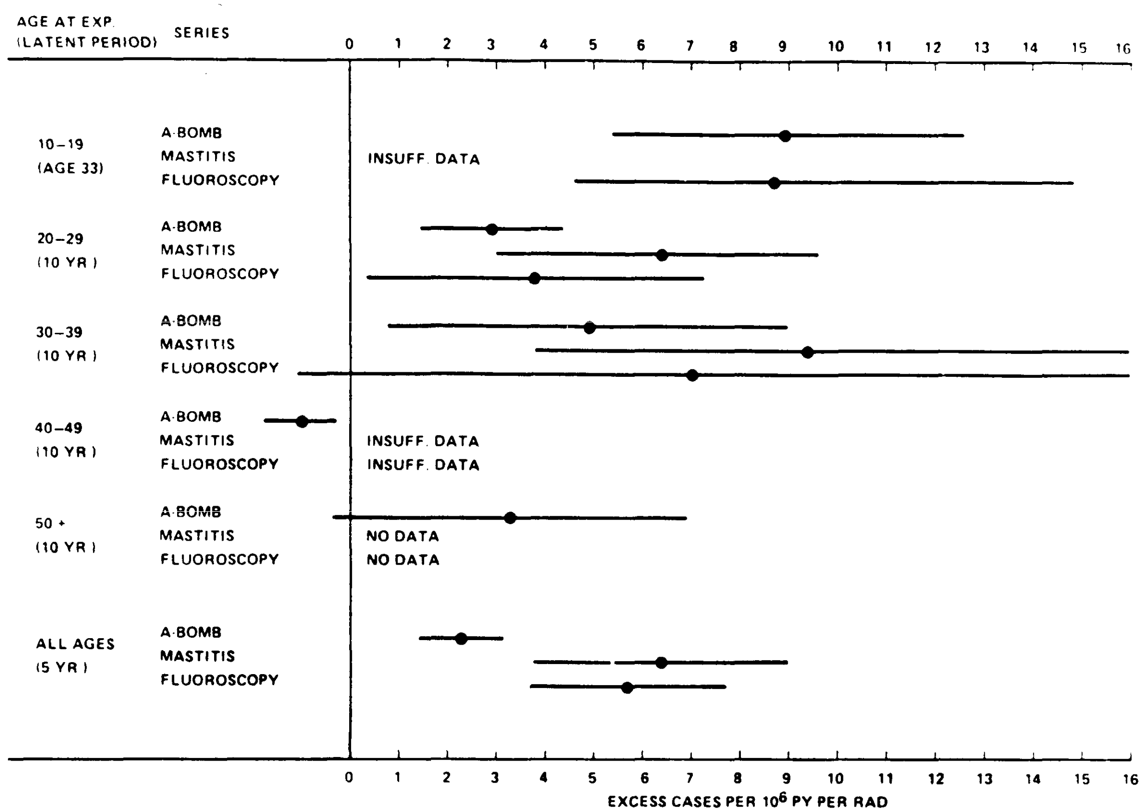
[a] Excess cases/10' women/rad/yr of life after assumed minimal latency periods of 20, 15, and 10 yr for ages 10–14, 15-19, and ≥20 yr at exposure, respectively.
[b] Excess risk per rad as a percentage of age-specific natural breast cancer risk.
[c] Estimate is based on small numbers; normal theory inference based on the estimate and its standard deviation may be misleading.
[d] Adjusted for differences between cities.

Age-Specific Risk Estimates

Linear estimates of absolute and relative risk for each series and each age at exposure represented in Appendix tables 1-3 are shown in table 9 and text-figure 9. The estimates are for risk following a minimum latency period (before substantial expression of risk) of 10 years for women 20 years or older at first exposure and 15 and 20 years for women 15-19 and 10-14 years old, respectively, at first exposure.

Remarkably, the absolute risk estimates for women exposed at ages 10-19, 20-29, and 30-39 years are similar among the three studies. Younger Japanese women appear to be as sensitive to radiation as are Western women in terms of absolute risk for radiogenic breast cancer. In terms of relative risk, the effect on Japanese women is, of course, greater inasmuch as they have approximately the same absolute risk as Western women but have a much lower natural breast cancer risk (text-fig. 2).

The negative risk coefficient for the LSS cohort of women 40 to 49 years old ATB underlines the complete absence of a dose reponse in this group. The positive coefficient ($P=$ 0.059 for absolute risk) for women 50 or



TEXT-FIGURE 9.—*L* model estimates of excess breast cancer risk per rad after latency period by age at exposure and series. *Horizontal bars* are normal theory 90% confidence intervals. EXP. = exposure; INSUFF. = insufficient; PY = person-yr.

more years of age ATB serves only to confuse the situation further. The extremely high coefficients for the Rochester mastitis patients 40-44 years of age at treatment are based on only 3 breast cancers among 14 exposed patients and do not, therefore, strongly suggest that the breast tissues of older women in this series were more sensitive to radiation than were those of younger women. They do, however, suggest that sensitivity to radiogenic breast cancer did not markedly decrease with increasing age at exposure. Unless some unknown artifact is responsible for the lack of a response in the LSS cohort of women 40-49 years of age ATB (and the negative risk coefficients might suggest the existence of such an artifact), the Japanese and American populations covered by these studies appear to differ in their breast cancer response to radiation received after the age of 40 years. The difference, if real, could be due to an effect of whole-body radiation on ovarian function or to some other factor.

The Swedish radiation therapy study of Baral et al. (6) reported a decreasing excess risk per rad, as compared to population rates, with increasing age at treatment. Dose was highly correlated with age at treatment, however, and average doses were very high: 285, 437, 667, 886, and 995 rads for women treated at ages 10-19, 20-29, 30-39, 40-49, and 50 or more years, respectively. It is not possible to tell if the variation in risk per rad by age at treatment was due to differences in sensitivity, to a high-dose cell killing effect like that suggested by the analysis of table 7 and text-figure 7, or even to variations by age with respect to the diseases treated.

Relative Versus Absolute Risk Models

Breast cancer risk depends on a woman's age at the time of observation; for women with histories of radiation exposure, risk may also depend on the age(s) at which the exposure occurred. Available data are far too sparse to yield reliable risk estimates calculated separately for specific combinations of age at exposure and age at risk. It is therefore convenient to assume that a woman's risk at one age has a simple relationship to her risk at another age on the basis that she received a certain radiation dose at a given age. An absolute risk model implies that the risk of breast cancer at a given age is the sum of the natural risk at that age plus a dose-dependent increment, which may depend on age at exposure but not on age at risk. The arithmetic difference between the risks for exposed women and otherwise similar nonexposed women remains constant over time. A relative risk model, however, expresses the probability of cancer at a given age as the product of the age-specific natural risk times a factor depending on dose and age at exposure. If incidence data based on a relatively short follow-up of women irradiated at young ages are used to estimate excess lifetime risk of breast cancer and if the natural incidence of breast cancer increases with advancing age throughout a woman's lifetime, then lifetime risk estimates based on relative risk models will tend to be greater than estimates based on corresponding absolute risk models. The correctness of either approach depends, of course, on the degree to which it represents the action of the unknown carcinogenic mechanism.

Differences and ratios of breast cancer rates observed among women exposed to high doses (≥ 100 rads) in each of the three series versus the appropriate population rates are shown in table 10 and text-figure 10 by age at risk for different ages at exposure. Although these data are not conclusive, they suggest that the rate ratios are at least as stable over time as the rate differences and perhaps more so. For the projection of risk to the end of life, or otherwise beyond the period of follow-up in these and other studies, it seems at least as appropriate to use the relative risk model as the absolute risk model.

However, virtually no information has been found on whether the excess breast cancer risk due to radiation exposure extends until the end of life. Such information is conspicuously lacking for women exposed at young ages for whom this excess has been high in both absolute and relative terms over the period of follow-up observed so far. A logical inconsistency occurs between the inference that relative risks may be constant over time following exposure and the inference that absolute risk may be invariant among populations exposed at similar ages but having different background breast cancer rates. As shown in text-figure 2, age-specific breast cancer rates for Japanese women differ markedly from those of American women, especially at postmenopausal ages. If absolute risks over the first 30 years of follow-up are equal for Japanese and American women exposed between the ages of 10 and 19 years, they should not, according to the relative risk projection model, be equal over the remainder of life. This contradiction, which conceivably could reflect ongoing changes in the age-specific breast cancer rates for Japan, is more likely to be an indication that neither the hypothesis of equal absolute risks for different irradiated populations of similar ages nor the hypotheses of constant relative risk over time is strictly true. Both hypotheses are extremely simple, and though each may be more nearly true than other equally simple hypotheses, they probably can be pushed too far. Further follow-up of the three exposed populations considered here should yield further insights.

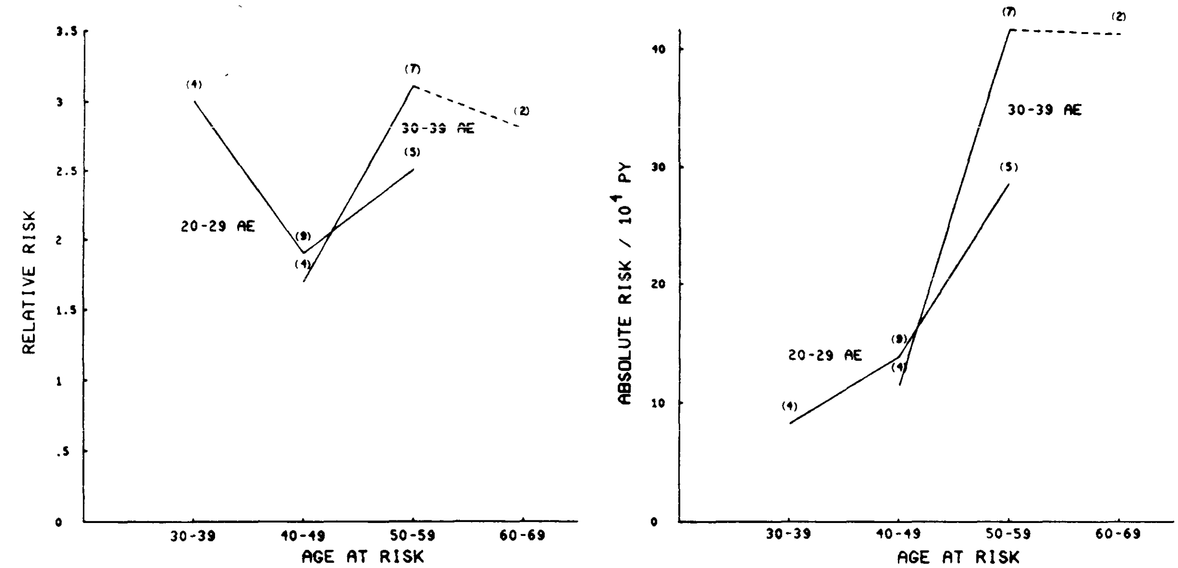
CONCLUSIONS

Breast cancer incidence data from three large popula-

TABLE 10.—*Comparisons of observed and expected breast cancer rates by series, age at exposure, and age at risk*

Series	Age at exposure, yr	Statistic	Age at observation at risk, yr					
			20–29	30–39	40–49	50–59	60–69	≥70
Rochester mastitis patients	20–29	Observed[a]		4	9	5		
		Observed/expected[b]		3.0	1.9	2.5		
		Difference[c]		8.2	13.9	28.6		
	30–39	Observed[a]			4	7	2	
		Observed/expected[b]			1.7	3.1	2.8	
		Difference[c]			11.5	41.6	41.2	
Massachusetts fluoroscopy patients	10–19	Observed[a]	1	4	7	3		
		Observed/expected[b]	9.0	4.1	3.1	3.1		
		Difference[c]	3.2	12.0	24.8	32.7		
	20–39	Observed[a]		2	10	7	5	
		Observed/expected[b]		1.1	1.7	1.2	2.1	
		Difference[c]		0.4	7.6	3.1	19.5	
LSS patients, 1950–74	10–19	Observed[d]	2	19	19			
		Observed/expected[e]	8.8	4.9	3.1			
		Difference[c]	0.6	4.6	7.7			
	20–29	Observed[d]		5	17	9		
		Observed/expected[e]		2.0	1.9	3.4		
		Difference[c]		1.1	3.4	7.0		
	30–39	Observed[d]			2	14	3	
		Observed/expected[e]			0.3	2.4	1.2	
		Difference[c]			−2.6	3.9	0.5	
	40–49	Observed[d]			2	4	5	1
		Observed/expected[e]			2.2	0.8	1.0	0.7
		Difference[c]			4.4	−0.5	0.1	−0.9
	≥50	Observed[d]				0	5	6
		Observed/expected[e]				0	1.8	1.6
		Difference[c]				−2.9	2.3	1.5

[a] Breast cancer cases among exposed women.
[b] Expected No. of breast cancers calculated according to age-specific population rates, Connecticut, 1963–65 (*16*).
[c] 10^4×(observed − expected)/WY at risk.
[d] Breast cancer cases among women exposed to ≥10 rads.
[e] Expected No. of breast cancers calculated according to age-specific population rates, Okayama Prefecture, 1966 (*16*).

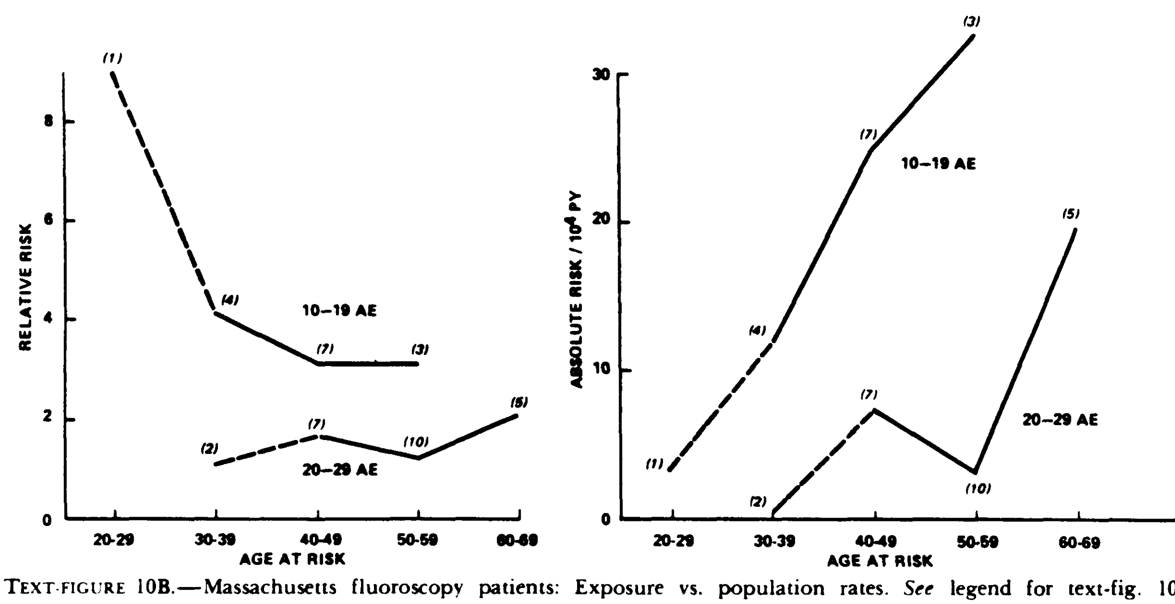


TEXT-FIGURE 10A.—Rochester mastitis patients: exposed vs. population rates. Comparisons of relative and absolute measures of breast cancer risk with respect to stability over time by series and age at exposure. No. of high-dose cases are given *in parentheses*. AE = age at exposure; PY = person-yr.

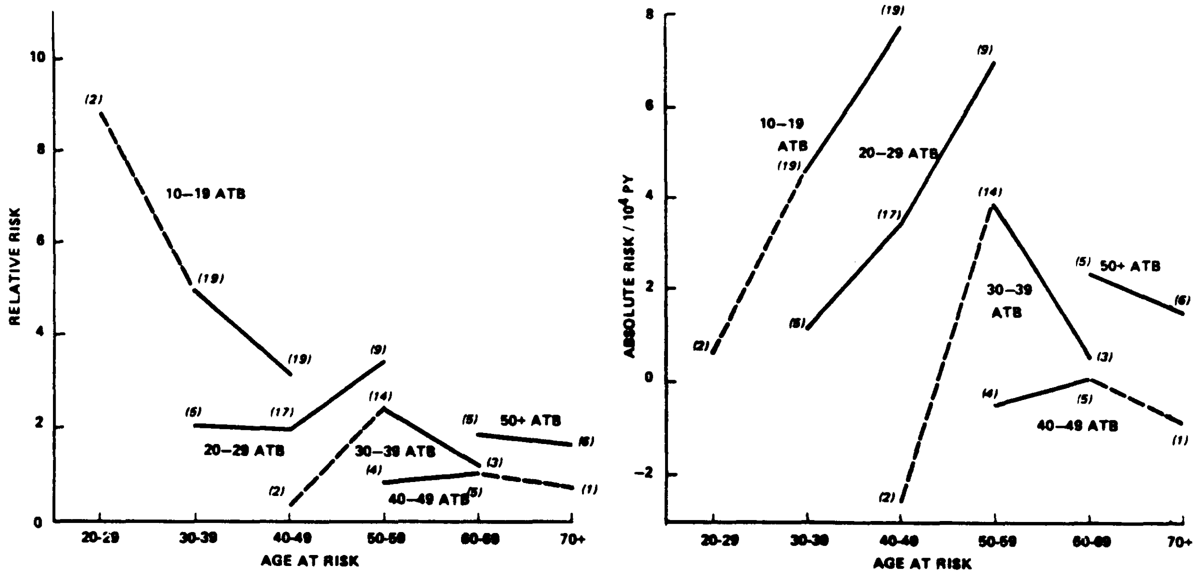
tions of irradiated women have been analyzed in parallel with respect to radiation dose. Particular attention has been paid to possible differences in dose response associated with radiation quality (neutrons vs. gamma rays), fractionation of dose, age at exposure, time after irradiation, age at observation for risk, and population differences in natural breast cancer risk.

The analyses confirmed the conclusions reached in earlier studies, including the original studies from which the present data were obtained. The analyses of age-adjusted breast cancer rates showed the dose-response curves to be consistent with linearity and provided little evidence of departures from linearity consistent with current radiobiologic theory. An analysis of Hiroshima and Nagasaki rates revealed little difference between the two cities regarding dose response, a finding consistent with approximate dose equivalence of neutrons and gamma rays with respect to radiation-induced breast cancer in women.

The age-specific analyses confirmed 1) the higher risk per rad after ages of normally high incidence were reached in women irradiated between the ages of 10 and 20 years and 2) the absence of any association between dose and risk previously reported for A-bomb survivors exposed between the ages of 40 and 49 years. This finding, the possibility of artifactual explanations related to whole-body exposure, and the paucity of data corresponding to comparable ages in the other two



TEXT-FIGURE 10B.—Massachusetts fluoroscopy patients: Exposure vs. population rates. *See* legend for text-fig. 10A.



TEXT-FIGURE 10C.—A-bomb survivors: ≥10 rads vs. population rates. *See* legend for text-fig. 10A.

series limit the age-specific generalizations possible from this study to the age range of 10-39 years at time of exposure. For intervals of age at exposure for which two or more series had sufficient data to compute risk estimates, i.e., 10-19, 20-29, and 30-39 years, estimates of absolute excess risk per rad were remarkably uniform across studies.

No association was found between dose and time from exposure until diagnosis of breast cancer for any of the three series; the temporal pattern of occurrence for radiation-attributable breast cancer appeared to be similar to that for breast cancer not attributable to radiation, e.g., in comparable low-dose group or nonexposed group or in the general population. In keeping with this observation, relative measures of excess risk due to radiation exposure appeared to be more stable over time than did absolute measures of risk. The relative risk model thus appeared to be more suitable than the absolute risk model for the projection, if not to the end of life, at least beyond the 30 or more years of follow-up represented by the data analyzed in this paper. Both projection models were used to estimate lifetime excess risk associated with the use of mammography in an earlier, more summary-type report based on these analyses (38).

The most significant finding of this study undoubtedly is that of linearity of the dose response for radiation-induced breast cancer. This finding is not based merely on linearity or near linearity of the observed dose-response curves. The approximate dose equivalence of gamma and neutron radiations is inconsistent with theoretical mechanisms of biologic effect requiring multiple, closely spaced ionizing events; the alternative, that a single ionizing event may eventually result in breast cancer, is consistent with linearity (*39*). The finding of approximately equal excess risks per rad for women of similar ages at exposure but with very different patterns of exposure—from the A-bomb survivors with a single exposure to the mastitis patients with 1-11 exposures to the TB patients with 100 or more exposures—also is strongly suggestive of linearity. The dose-response curve for multiple, widely spaced, low-dose exposures to low-LET radiation might be expected to be linear to the extent that the effects of separate ionizing events are independent; e.g., independence would obtain if a single ionizing event could result eventually in cancer or if the effects of spatially separated ionizing events were subject to prompt repair. Only the first of these possibilities, however, is consistent with approximate equivalence of effect between a single 100-rad exposure and 100 temporally separated 1-rad exposures. This approximate equivalence, because it involves three distinct irradiated populations, seems unlikely to be coincidental. Brown (*40*) previously remarked on the similarity of risk estimates based on earlier breast cancer series and its implication for linearity.

Only approximate linearity is claimed to hold. Some degree of curvilinearity is consistent with these data, and in one of the three series there was a suggestion of a high-dose downturn in the dose-response relationship. It is claimed, however, that any true deviations from linearity probably are not so marked as to cause estimates obtained under the assumption of linearity to be seriously wrong. Thus, for example, the age-specific linear regression coefficients in table 9 are estimates not only of the average risks per rad for exposures over the dose ranges represented by the data, which they would be even if the true dose response function were nonlinear, but also of the excess risk from a single 1-rad exposure, a status they could have only under linearity.

The second most significant finding concerns the temporal pattern after exposure of radiation-induced breast cancer and its relationship to age-specific population risk patterns. There are too few data on women exposed at older ages, and follow-up for women exposed at younger ages is too short to tell whether the observed relationships hold throughout life. A possible conclusion is that radiation-induced breast cancer is subject to many, if not all, of the factors that determine the occurrence of breast cancer in unirradiated populations. If, as it seems, the appearance time of a radiation-induced breast cancer is determined by hormones or other host factors that also determine the appearance time of other breast cancers, perhaps the timing of "primary" causes of breast cancer, other than radiation, also has little to do with the time of diagnosis. If radiation exposures between the ages of 10 and 19 years produce more breast cancer than do equivalent exposures at later ages and if the resultant excess risk continues until late in life, maybe the causal events for a disproportionate number of breast cancers among unirradiated women occur during adolescence and early life, as suggested by MacMahon et al. *(15)*.

Finally, some of the findings of this analysis, in particular the crucial finding of equivalent age-specific risk estimates over the range of ages 10-39 years at time of exposure from the three study populations, could not have been deduced from the original published studies. Where other such parallel reanalyses of dose-response data from different studies are possible, they seem definitely worthwhile.

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APPENDIX

APPENDIX TABLE 1.—*Rochester mastitis study: Number of breast cancer patients and WY at risk by radiation dose, age at treatment, and period of observation*

Age at treatment, yr	Observation period; yr since treatment	Dose, in rads, to breast: 0	40–99	100–199	200–299	300–399	≥400	Total
		No. of breast cancer patients						
15–19	5–9	0	0	0	0	0	0	0
	10–14	0	0	0	0	0	0	0
	15–19	0	0	0	0	0	0	0
	≥20	0	0	1	0	1	0	2
	Total	0	0	1	0	1	0	2
20–24	5–9	0	0	0	0	0	0	0
	10–14	1	0	0	0	0	0	1
	15–19	1	0	0	0	0	0	1
	≥20	3	0	1	2	2	0	8
	Total	5	0	1	2	2	0	10
25–29	5–9	0	0	0	0	0	0	0
	10–14	1	0	2	0	0	2	5
	15–19	5	0	1	1	0	0	7
	≥20	3	0	2	3	1	1	10
	Total	9	0	5	4	1	3	22
30–34	5–9	1	0	0	0	0	0	1
	10–14	3	0	1	0	1	0	5
	15–19	2	1	1	0	0	1	5
	≥20	3	0	2	1	1	1	8
	Total	9	1	4	1	2	2	19
35–39	5–9	3	0	0	0	0	0	3
	10–14	1	0	1	1	0	0	3
	15–19	2	0	0	0	0	0	2
	≥20	2	0	0	1	0	0	3
	Total	8	0	1	2	0	0	11
40–44	5–9	0	0	0	0	0	0	0
	10–14	0	0	0	0	0	1	1
	15–19	0	0	0	0	0	0	0
	≥20	1	0	1	0	1	0	3
	Total	1	0	1	0	1	1	4
Total	5–9	4	0	0	0	0	0	4
	10–14	6	0	4	1	1	3	15
	15–19	10	1	2	1	0	1	15
	≥20	12	0	7	7	6	2	34
	Total	32	1	13	9	7	6	68
		WY at risk						
15–19	5–9	174	10	45	35	15	20	299
	10–14	165	10	45	35	15	20	290
	15–19	141	10	45	34	15	20	265
	≥20	238	21	67	38	12	29	405
	Total	718	51	202	142	57	89	1,259
20–24	5–9	1,263	60	275	220	105	90	2,013
	10–14	1,205	60	274	220	105	90	1,954
	15–19	1,113	60	249	209	102	90	1,823
	≥20	1,897	80	358	290	158	125	2,908
	Total	5,478	260	1,156	939	470	395	8,698
25–29	5–9	1,711	85	435	260	140	175	2,806
	10–14	1,606	85	431	260	140	173	2,695
	15–19	1,444	77	395	255	135	159	2,465
	≥20	2,579	81	519	342	176	232	3,929
	Total	7,340	328	1,780	1,117	591	739	11,895

APPENDIX TABLE 1 (continued).—*Rochester mastitis study: Number of breast cancer patients and WY at risk by radiation dose, age at treatment, and period of observation*

Age at treatment, yr	Observation period; yr since treatment	Dose, in rads, to breast						
		0	40–99	100–199	200–299	300–399	≥400	Total
		WY at risk						
30–34	5–9	1,180	55	219	170	45	85	1,754
	10–14	1,112	54	212	170	45	84	1,677
	15–19	986	44	200	162	40	79	1,511
	≥20	1,636	64	281	227	60	80	2,348
	Total	4,914	217	912	729	190	328	7,290
35–39	5–9	445	15	75	75	20	35	665
	10–14	408	15	74	69	20	35	621
	15–19	360	15	65	58	20	34	552
	≥20	592	28	115	83	30	46	894
	Total	1,805	73	329	285	90	150	2,732
40–44	5–9	110	5	20	15	15	10	175
	10–14	100	5	20	15	15	9	164
	15–19	78	5	20	15	15	5	138
	≥20	107	7	24	16	7	9	170
	Total	395	22	84	61	52	33	647
Total	5–9	4,883	230	1,069	760	340	415	7,712
	10–14	4,596	229	1,056	754	340	411	7,401
	15–19	4,122	229	1,056	754	340	411	7,401
	≥20	7,049	281	1,364	980	443	521	10,654
	Total	20,650	951	4,463	3,212	1,450	1,734	32,521

APPENDIX TABLE 2.—*Massachusetts fluoroscopy study: Number of breast cancer patients and WY at risk by radiation dose, by age at first treatment, and by period of observation*

Age at treatment, yr	Observation period; yr since treatment	Dose, in rads, to breast						
		0	40–99	100–199	200–299	300–399	≥400	Total
		No. of breast cancer patients						
10–14	5–9	0	0	0	0	0	0	0
	10–14	0	0	0	0	0	0	0
	15–19	0	0	0	1	0	0	1
	≥20	3	0	0	0	1	0	4
	Total	3	0	0	1	1	0	5
15–19	5–9	0	0	0	0	0	0	0
	10–14	0	1	0	0	0	0	1
	15–19	0	0	0	0	0	1	1
	≥20	1	2	4	4	1	0	12
	Total	1	3	4	4	1	1	14
20–24	5–9	0	0	0	0	0	0	0
	10–14	0	0	0	0	0	0	0
	15–19	0	0	0	3	0	0	3
	≥20	2	2	2	0	0	2	8
	Total	2	2	2	3	0	2	11
25–29	5–9	0	0	0	0	0	0	0
	10–14	1	0	0	0	0	0	1
	15–19	0	0	0	0	0	0	0
	≥20	3	2	4	2	1	0	12
	Total	4	2	4	2	1	0	13
30–34	5–9	1	1	0	0	0	0	2
	10–14	0	0	0	0	0	0	0
	15–19	0	0	0	0	0	0	0
	≥20	0	2	0	1	0	0	3
	Total	1	3	0	1	0	0	5
35–39	5–9	2	0	0	0	0	1	3
	10–14	0	0	1	0	0	0	1
	15–19	0	0	0	0	0	0	0
	≥20	0	0	0	0	0	0	0
	Total	2	0	1	0	0	1	4
40–44	5–9	0	0	0	0	0	0	0
	10–14	0	0	0	0	0	0	0
	15–19	0	0	0	0	0	0	0
	≥20	1	0	1	0	0	0	2
	Total	1	0	1	0	0	0	2

APPENDIX TABLE 2 (continued).—*Massachusetts fluoroscopy study: Number of breast cancer patients and WY at risk by radiation dose, by age at first treatment, and by period of observation*

Age at treatment, yr	Observation period; yr since treatment	Dose, in rads, to breast						
		0	40–99	100–199	200–299	300–399	≥400	Total
		No. of breast cancer patients						
Total	5–9	3	1	0	0	0	1	5
	10–14	1	1	1	0	0	0	3
	15–19	0	0	0	4	0	1	5
	≥20	10	8	11	7	3	2	41
	Total	14	10	12	11	3	4	54
		WY at risk						
10–14	5–9	860	124	77	100	50	39	1,250
	10–14	816	110	75	96	47	35	1,179
	15–19	781	110	72	93	45	34	1,135
	≥20	2,492	244	187	282	131	99	3,435
	Total	4,949	588	411	571	273	207	6,999
15–19	5–9	587	311	304	192	85	101	1,580
	10–14	560	297	286	190	80	95	1,508
	15–19	544	288	276	190	77	92	1,467
	≥20	1,502	737	733	481	229	263	3,945
	Total	3,193	1,633	1,599	1,053	471	551	8,500
20–24	5–9	429	414	321	211	71	91	1,537
	10–14	416	377	306	210	70	81	1,460
	15–19	399	360	301	200	70	80	1,410
	≥20	808	911	708	596	206	221	3,450
	Total	2,052	2,062	1,636	1,217	417	473	7,857
25–29	5–9	426	420	194	170	76	30	1,316
	10–14	388	401	183	165	68	26	1,231
	15–19	366	399	176	165	65	25	1,196
	≥20	821	875	445	499	198	69	2,907
	Total	2,001	2,095	998	999	407	150	6,650
30–34	5–9	338	211	141	70	15	10	785
	10–14	312	204	137	70	15	10	748
	15–19	301	199	127	70	12	5	714
	≥20	695	468	268	163	29	5	1,628
	Total	1,646	1,082	673	373	71	30	3,875
35–39	5–9	247	168	75	65	5	8	568
	10–14	233	155	71	62	5	5	531
	15–19	220	143	70	60	5	5	503
	≥20	412	258	125	182	13	0	990
	Total	1,112	724	341	369	28	18	2,592
40–44	5–9	194	176	57	30	5	0	462
	10–14	171	150	49	28	5	0	403
	15–19	145	140	35	20	5	0	345
	≥20	228	219	63	50	15	0	575
	Total	738	685	204	128	30	0	1,785
Total	5–9	3,081	1,824	1,169	838	307	279	7,498
	10–14	2,896	1,694	1,107	821	290	252	7,060
	15–19	2,756	1,639	1,057	798	279	241	6,770
	≥20	6,958	3,712	2,529	2,253	821	657	16,930
	Total	15,691	8,869	5,862	4,710	1,697	1,429	38,258

APPENDIX TABLE 3A.—*RERF LSS sample series, A-bomb survivors 1950–74: Number of breast cancers by city, radiation dose, age ATB, and period of observation*

Age ATB, yr	Observation period	Dose, in rads, to breast										
		0	1–3	4–9	10–19	20–49	50–99	100–199	200–299	300–399	≥400	Total
		No. of breast cancers in Nagasaki										
0–4	1950–54	0	0	0	0	0	0	0	0	0	0	0
	1955–59	0	0	0	0	0	0	0	0	0	0	0
	1960–64	0	0	0	0	0	0	0	0	0	0	0
	1965–69	0	0	0	0	0	0	0	0	0	0	0
	1970–74	0	0	0	0	0	0	0	0	0	0	0
	Total	0	0	0	0	0	0	0	0	0	0	0

APPENDIX TABLE 3A (continued).—*RERF LSS sample series, A-bomb survivors 1950–74: Number of breast cancers by city, radiation dose, age ATB, and period of observation*

Age ATB, yr	Observation period	Dose, in rads, to breast										
		0	1–3	4–9	10–19	20–49	50–99	100–199	200–299	300–399	≥400	Total
		No. of breast cancers in Nagasaki										
5–9	1950–54	0	0	0	0	0	0	0	0	0	0	0
	1955–59	0	0	0	0	0	0	0	0	0	0	0
	1960–64	0	0	0	0	0	0	0	0	0	0	0
	1965–69	0	0	0	0	0	1	0	0	0	0	1
	1970–74	0	0	0	0	0	0	0	0	0	0	0
	Total	0	0	0	0	0	1	0	0	0	0	1
10–14	1950–54	0	0	0	0	0	0	0	0	0	0	0
	1955–59	0	0	0	0	0	0	0	0	0	0	0
	1960–64	0	0	0	0	0	0	1	0	0	0	1
	1965–69	1	0	0	1	2	0	1	0	0	1	6
	1970–74	0	1	0	0	0	1	0	1	0	0	3
	Total	1	1	0	1	2	1	2	1	0	1	10
15–19	1950–54	1	0	0	0	0	0	0	0	0	0	1
	1955–59	0	0	0	0	0	0	0	0	0	0	0
	1960–64	0	0	0	0	0	0	0	0	0	0	0
	1965–69	0	0	0	0	0	1	1	1	0	0	3
	1970–74	3	1	0	0	0	0	1	0	0	0	5
	Total	4	1	0	0	0	1	2	1	0	0	9
20–24	1950–54	0	0	0	0	0	0	0	0	0	0	0
	1955–59	0	0	0	0	0	0	1	0	0	0	1
	1960–64	0	0	1	0	0	0	0	0	0	0	1
	1965–69	2	0	0	0	0	0	0	0	0	2	4
	1970–74	1	0	0	0	0	0	1	0	0	0	2
	Total	3	0	1	0	0	0	2	0	0	2	8
25–29	1950–54	0	1	0	0	0	0	0	0	0	0	1
	1955–59	0	0	1	0	0	0	0	0	0	0	1
	1960–64	2	0	1	0	1	0	0	0	0	0	4
	1965–69	1	1	0	1	0	0	1	0	0	0	4
	1970–74	2	0	0	0	0	1	1	1	0	0	5
	Total	5	2	2	1	1	1	2	1	0	0	15
30–34	1950–54	0	0	0	1	0	0	0	0	0	0	1
	1955–59	2	0	0	0	0	0	0	0	0	0	2
	1960–64	1	0	0	0	0	0	0	0	0	0	1
	1965–69	0	0	0	0	0	0	0	0	1	0	1
	1970–74	3	0	0	0	0	0	0	1	0	0	4
	Total	6	0	0	1	0	0	0	1	1	0	9
35–39	1950–54	0	0	1	0	0	0	0	0	0	0	1
	1955–59	0	0	0	0	0	0	1	1	0	0	2
	1960–64	0	1	0	0	0	0	0	0	0	0	1
	1965–69	0	0	0	0	0	0	0	0	0	0	0
	1970–74	0	0	0	0	0	0	0	0	0	0	0
	Total	0	1	1	0	0	0	1	1	0	0	4
40–44	1950–54	0	0	1	0	0	0	0	0	0	0	1
	1955–59	0	0	0	0	0	0	0	0	0	0	0
	1960–64	0	0	0	1	0	0	0	0	0	0	1
	1965–69	2	0	0	0	0	0	0	0	0	0	2
	1970–74	0	0	0	0	0	0	0	0	0	0	0
	Total	2	0	1	1	0	0	0	0	0	0	4
45–49	1950–54	0	0	0	0	0	0	0	0	0	0	0
	1955–59	1	0	0	0	0	0	0	0	0	0	1
	1960–64	0	0	0	0	0	0	0	0	0	0	0
	1965–69	0	0	0	0	0	0	0	0	0	0	0
	1970–74	0	0	0	0	0	0	0	0	0	0	0
	Total	1	0	0	0	0	0	0	0	0	0	1
≥50	1950–54	0	0	0	0	0	0	1	0	0	0	1
	1955–59	1	1	1	0	1	0	0	0	0	0	4
	1960–64	0	1	0	0	1	0	0	0	0	0	2
	1965–69	0	0	0	0	0	0	0	0	0	0	0
	1970–74	0	0	0	0	0	0	0	0	0	0	0
	Total	1	2	1	0	2	0	1	0	0	0	7
Total	1950–54	1	1	2	1	0	0	1	0	0	0	6
	1955–59	4	1	2	0	1	0	2	1	0	0	11
	1960–64	3	2	2	1	2	0	1	0	0	0	11
	1965–69	6	1	0	2	2	2	3	1	1	3	21
	1970–74	9	2	0	0	0	2	3	3	0	0	19
	Total	23	7	6	4	5	4	10	5	1	3	68

APPENDIX TABLE 3A (continued).—*RERF LSS sample series, A-bomb survivors 1950–74: Number of breast cancers by city, radiation dose, age ATB, and period of observation*

Age ATB, yr	Observation period	Dose, in rads, to breast										
		0	1–3	4–9	10–19	20–49	50–99	100–199	200–299	300–399	≥400	Total
		No. of breast cancers in Hiroshima										
0–4	1950–54	0	0	0	0	0	0	0	0	0	0	0
	1955–59	0	0	0	0	0	0	0	0	0	0	0
	1960–64	0	0	0	0	0	0	0	0	0	0	0
	1965–69	0	0	0	0	0	0	0	0	0	0	0
	1970–74	2	0	0	0	0	0	0	0	0	0	2
	Total	2	0	0	0	0	0	0	0	0	0	2
5–9	1950–54	0	0	0	0	0	0	0	0	0	0	0
	1955–59	0	0	0	0	0	0	0	0	0	0	0
	1960–64	0	0	0	0	0	0	0	0	0	0	0
	1965–69	1	0	1	0	0	0	0	0	0	0	2
	1970–74	0	0	0	0	0	0	0	0	0	0	0
	Total	1	0	1	0	0	0	0	0	0	0	2
10–14	1950–54	0	0	0	0	0	0	0	0	0	0	0
	1955–59	0	0	0	0	0	0	0	0	0	0	0
	1960–64	1	0	0	2	0	0	0	0	0	0	3
	1965–69	2	0	0	1	1	1	1	0	0	0	6
	1970–74	5	0	1	0	0	1	0	0	0	1	8
	Total	8	0	1	3	1	2	1	0	0	1	17
15–19	1950–54	0	0	0	0	0	0	0	0	0	0	0
	1955–59	0	0	0	0	0	0	0	0	0	0	0
	1960–64	3	0	0	0	3	1	0	0	0	2	9
	1965–69	10	0	1	0	0	1	1	0	0	0	13
	1970–74	5	2	2	1	0	1	2	1	0	2	16
	Total	18	2	3	1	3	3	3	1	0	4	38
20–24	1950–54	0	0	0	0	0	0	0	0	0	0	0
	1955–59	0	0	0	0	0	0	0	0	0	0	0
	1960–64	7	0	0	1	0	1	0	1	0	0	10
	1965–69	7	2	0	0	1	1	0	1	0	0	12
	1970–74	6	0	1	0	2	0	0	0	1	0	10
	Total	20	2	1	1	3	2	0	2	1	0	32
25–29	1950–54	0	0	0	0	0	0	1	0	0	0	1
	1955–59	3	0	0	0	0	0	0	0	0	0	3
	1960–64	5	1	0	1	1	1	0	0	0	0	9
	1965–69	2	1	0	0	1	1	1	0	0	0	6
	1970–74	5	0	1	0	1	0	0	0	0	0	7
	Total	16	2	1	1	3	2	2	0	0	0	27
30–34	1950–54	0	0	0	0	0	0	0	0	0	0	0
	1955–59	5	0	0	0	0	0	0	0	0	0	5
	1960–64	6	1	0	1	0	0	1	0	0	0	9
	1965–69	3	2	0	0	1	0	2	0	1	0	9
	1970–74	7	2	0	0	1	0	0	0	0	0	10
	Total	21	5	0	1	3	0	3	0	1	0	34
35–39	1950–54	2	2	0	0	0	0	0	0	0	0	4
	1955–59	8	0	0	0	1	1	0	0	0	0	10
	1960–64	3	2	1	0	1	0	1	0	0	0	8
	1965–69	5	0	0	1	0	0	1	0	1	1	9
	1970–74	4	1	0	0	0	0	0	0	0	0	5
	Total	22	5	1	1	2	1	2	0	1	1	36
40–44	1950–54	2	1	1	2	0	1	0	0	0	0	7
	1955–59	4	2	0	0	0	0	0	0	0	0	6
	1960–64	5	0	0	1	0	0	0	0	0	0	6
	1965–69	4	1	1	0	0	0	0	0	0	0	6
	1970–74	2	1	2	0	0	0	0	0	0	0	5
	Total	18	5	4	3	0	1	0	0	0	0	31
45–49	1950–54	3	0	1	1	1	0	0	0	0	0	6
	1955–59	5	0	1	0	0	0	1	0	0	0	7
	1960–64	3	0	0	0	2	0	0	0	0	0	5
	1965–69	3	0	0	2	0	0	0	0	0	0	5
	1970–74	3	0	0	0	0	0	0	0	0	0	3
	Total	17	0	2	3	3	0	1	0	0	0	26
≥50	1950–54	3	0	0	1	0	0	0	0	0	0	4
	1955–59	5	0	0	1	0	1	1	0	0	0	8
	1960–64	11	0	1	1	1	0	1	0	0	0	15
	1965–69	4	0	0	0	0	0	0	0	0	0	4
	1970–74	2	2	1	0	1	0	0	0	0	0	6
	Total	25	2	2	4	2	1	2	0	0	0	38

APPENDIX TABLE 3A (continued).—*RERF LSS sample series, A-bomb survivors 1950–74: Number of breast cancers by city, radiation dose, age ATB, and period of observation*

Age ATB, yr	Observation period	Dose, in rads, to breast										
		0	1–3	4–9	10–19	20–49	50–99	100–199	200–299	300–399	≥400	Total
		No. of breast cancers in Hiroshima										
Total	1950–54	10	3	2	4	1	1	1	0	0	0	22
	1955–59	30	2	1	1	1	2	2	0	0	0	39
	1960–64	44	4	2	7	8	3	3	1	0	2	74
	1965–69	41	6	3	4	4	4	6	1	2	1	72
	1970–74	41	8	8	1	5	2	2	1	1	3	72
	Total	168	23	16	18	20	12	14	3	3	6	283

APPENDIX TABLE 3B.—*RERF LSS sample series, A-bomb survivors 1950–74: WY at risk by city, radiation dose, age ATB, and period of observation*

Age ATB, yr	Observation period	Dose, in rads, to breast										
		0	1–3	4–9	10–19	20–49	50–99	100–199	200–299	300–399	≥400	Total
		WY at risk in Nagasaki										
0–4	1950–54	2,605	769	895	608	412	230	187	38	47	54	5,845
	1955–59	3,065	905	1,046	715	477	270	220	45	55	51	6,847
	1960–64	3,057	896	1,045	711	475	270	220	45	55	50	6,823
	1965–69	3,040	893	1,041	710	475	270	216	45	55	50	6,794
	1970–74	3,031	883	1,040	707	471	270	215	45	55	50	6,766
	Total	14,798	4,345	5,066	3,450	2,309	1,310	1,058	218	267	255	33,075
5–9	1950–54	2,961	883	727	570	378	272	174	85	34	55	6,139
	1955–59	3,456	1,025	854	670	433	318	204	100	40	61	7,158
	1960–64	3,439	1,020	850	670	430	315	200	100	40	60	7,124
	1965–69	3,408	1,019	847	660	426	312	200	100	40	60	7,070
	1970–74	3,371	1,015	843	655	421	310	200	100	40	60	7,015
	Total	16,635	4,961	4,120	3,225	2,087	1,526	978	485	194	296	34,505
10–14	1950–54	3,429	984	977	642	423	332	602	157	47	38	7,629
	1955–59	3,984	1,130	1,130	755	491	390	699	178	55	45	8,855
	1960–64	3,966	1,119	1,125	755	487	390	688	175	55	45	8,803
	1965–69	3,944	1,109	1,119	745	483	386	681	175	55	45	8,740
	1970–74	3,928	1,097	1,101	738	470	380	666	175	55	45	8,654
	Total	19,250	5,439	5,450	3,634	2,352	1,878	3,335	859	267	218	42,680
15–19	1950–54	5,075	879	713	443	419	662	945	336	77	67	9,615
	1955–59	5,913	1,019	821	513	488	773	1,109	385	90	75	11,184
	1960–64	5,848	995	815	509	485	770	1,099	377	90	75	11,062
	1965–69	5,790	984	811	505	485	770	1,082	366	90	73	10,955
	1970–74	5,727	976	802	503	483	770	1,071	362	90	70	10,854
	Total	28,353	4,853	3,961	2,472	2,359	3,744	5,305	1,826	437	359	53,668
20–24	1950–54	3,170	655	599	403	299	332	476	187	68	70	6,258
	1955–59	3,676	768	699	470	340	390	560	215	72	80	7,269
	1960–64	3,637	759	689	467	331	390	557	214	70	80	7,192
	1965–69	3,612	745	676	460	330	378	540	210	64	80	7,093
	1970–74	3,557	735	657	454	330	358	527	209	60	80	6,965
	Total	17,651	3,661	3,318	2,253	1,629	1,847	2,660	1,034	333	390	34,776
25–29	1950–54	1,923	537	550	328	276	196	190	80	47	21	4,149
	1955–59	2,233	617	634	385	324	226	220	90	53	25	4,805
	1960–64	2,190	609	617	385	318	216	220	90	50	25	4,718
	1965–69	2,127	601	595	380	311	206	217	90	49	25	4,600
	1970–74	2,073	598	569	376	301	198	215	90	45	25	4,487
	Total	10,545	2,960	2,964	1,853	1,529	1,042	1,061	440	243	121	22,758
30–34	1950–54	1,867	512	513	421	268	197	130	20	38	34	3,998
	1955–59	2,166	583	588	471	307	221	145	20	41	39	4,580
	1960–64	2,115	567	577	456	301	218	142	20	40	35	4,469
	1965–69	2,038	554	564	433	300	215	140	20	40	35	4,338
	1970–74	1,967	538	543	418	290	215	140	20	35	35	4,200
	Total	10,152	2,754	2,784	2,198	1,465	1,064	696	100	193	178	21,583

APPENDIX TABLE 3B (continued).—*RERF LSS sample series, A-bomb survivors 1950–74: WY at risk by city, radiation dose, age ATB, and period of observation*

Age ATB, yr	Observation period	Dose, in rads, to breast										
		0	1–3	4–9	10–19	20–49	50–99	100–199	200–299	300–399	≥400	Total
		WY at risk in Nagasaki										
35–39	1950–54	1,761	527	520	391	255	196	119	66	34	47	3,915
	1955–59	2,012	601	587	455	298	230	136	74	40	55	4,486
	1960–64	1,935	568	546	441	285	222	135	70	40	55	4,295
	1965–69	1,843	539	506	407	283	212	123	70	40	55	4,076
	1970–74	1,760	504	472	365	271	206	116	65	32	47	3,837
	Total	9,310	2,738	2,630	2,058	1,391	1,065	628	344	186	259	20,607
40–44	1950–54	1,515	554	481	328	237	162	126	38	17	21	3,478
	1955–59	1,736	623	543	361	265	186	134	45	20	23	3,934
	1960–64	1,659	574	520	346	246	185	125	44	20	20	3,736
	1965–69	1,527	520	482	333	225	178	125	39	20	20	3,468
	1970–74	1,382	469	438	301	187	173	124	29	20	16	3,137
	Total	7,819	2,739	2,463	1,669	1,158	883	633	194	97	99	17,752
45–49	1950–54	1,287	636	486	341	168	136	138	38	27	26	3,283
	1955–59	1,442	720	523	379	182	155	151	44	30	27	3,652
	1960–64	1,347	655	463	348	170	149	144	35	29	25	3,362
	1965–69	1,235	593	415	307	156	136	131	35	25	25	3,057
	1970–74	1,060	513	372	260	118	123	107	35	24	22	2,632
	Total	6,370	3,116	2,259	1,634	793	698	671	187	134	124	15,985
≥50	1950–54	2,469	950	1,035	613	369	251	246	46	26	32	6,036
	1955–59	2,319	907	1,003	611	339	249	236	42	30	27	5,761
	1960–64	1,715	687	776	461	245	193	178	33	22	17	4,323
	1965–69	1,224	499	585	287	162	129	123	26	15	14	3,062
	1970–74	758	327	356	162	102	86	80	13	14	6	1,900
	Total	8,484	3,368	3,754	2,133	1,216	907	861	158	106	95	21,081
Total	1950–54	28,062	7,885	7,495	5,087	3,502	2,963	3,332	1,090	461	465	60,343
	1955–59	32,000	8,896	8,425	5,785	3,941	3,406	3,812	1,237	525	506	68,529
	1960–64	30,906	8,446	8,020	5,545	3,770	3,317	3,706	1,201	510	487	65,905
	1965–69	29,786	8,054	7,638	5,226	3,633	3,190	3,576	1,175	492	481	63,249
	1970–74	28,612	7,653	7,191	4,936	3,442	3,087	3,459	1,141	469	455	60,444
	Total	149,365	40,933	38,768	26,578	18,288	15,962	17,883	5,844	2,456	2,394	318,469
		WY at risk in Hiroshima										
0–4	1950–54	11,895	1,561	1,181	1,401	1,068	421	223	102	43	38	17,931
	1955–59	16,029	1,833	1,380	1,642	1,255	495	260	120	50	45	23,107
	1960–64	15,995	1,830	1,372	1,640	1,255	490	260	120	50	45	23,056
	1965–69	15,940	1,828	1,370	1,640	1,255	490	260	120	50	45	22,996
	1970–74	15,881	1,821	1,370	1,634	1,254	485	256	120	50	45	22,915
	Total	75,739	8,871	6,673	7,956	6,087	2,380	1,258	582	243	218	110,005
5–9	1950–54	7,727	965	710	820	544	286	200	43	26	21	11,341
	1955–59	9,863	1,135	827	965	632	335	235	50	30	25	14,096
	1960–64	9,803	1,121	825	961	626	335	234	50	30	25	14,009
	1965–69	9,768	1,116	825	960	625	333	230	50	26	25	13,957
	1970–74	9,728	1,115	825	960	625	325	230	50	25	25	13,908
	Total	46,889	5,451	4,012	4,666	3,052	1,614	1,128	243	136	121	67,309
10–14	1950–54	8,382	1,154	742	1,189	599	517	264	249	47	26	13,168
	1955–59	11,516	1,348	869	1,390	700	600	310	290	55	30	17,107
	1960–64	11,424	1,339	865	1,381	697	580	310	290	55	30	16,968
	1965–69	11,347	1,335	848	1,373	693	575	301	290	55	30	16,843
	1970–74	11,270	1,330	835	1,355	686	575	291	278	55	25	16,698
	Total	53,938	6,505	4,158	6,686	3,373	2,846	1,475	1,397	267	140	80,783
15–19	1950–54	12,517	2,035	1,258	1,537	1,081	714	416	145	72	111	19,886
	1955–59	17,891	2,372	1,475	1,798	1,250	840	478	168	85	130	26,485
	1960–64	17,747	2,354	1,458	1,784	1,220	839	468	165	85	130	26,248
	1965–69	17,623	2,342	1,439	1,771	1,190	829	461	165	85	130	26,033
	1970–74	17,477	2,337	1,420	1,756	1,177	818	456	163	85	125	25,811
	Total	83,254	11,438	7,049	8,645	5,917	4,040	2,277	805	412	625	124,462
20–24	1950–54	10,586	1,657	1,105	1,201	1,044	664	361	170	111	92	16,990
	1955–59	14,577	1,923	1,283	1,394	1,216	775	420	198	130	101	22,014
	1960–64	14,418	1,905	1,263	1,386	1,192	770	415	195	126	96	21,764
	1965–69	14,270	1,878	1,250	1,365	1,183	762	409	193	121	93	21,521
	1970–74	14,078	1,857	1,224	1,349	1,158	751	399	184	115	90	21,203
	Total	67,928	9,219	6,124	6,694	5,792	3,721	2,003	939	602	470	103,492
25–29	1950–54	8,949	1,285	1,033	1,096	903	443	266	106	51	47	14,179
	1955–59	12,158	1,488	1,195	1,278	1,053	516	304	123	60	55	18,228
	1960–64	12,022	1,464	1,183	1,267	1,032	505	290	116	60	55	17,991

APPENDIX TABLE 3B (continued).—*RERF LSS sample series, A-bomb survivors 1950–74: WY at risk by city, radiation dose, age ATB, and period of observation*

Age ATB, yr	Observation period	Dose, in rads, to breast										
		0	1–3	4–9	10–19	20–49	50–99	100–199	200–299	300–399	≥400	Total
		WY at risk in Hiroshima										
	1965–69	11,870	1,434	1,174	1,248	1,020	489	281	110	57	55	17,735
	1970–74	11,649	1,405	1,147	1,219	993	477	274	104	55	53	17,374
	Total	56,647	7,075	5,730	6,108	4,999	2,429	1,414	559	283	264	85,507
30–34	1950–54	9,367	1,338	1,032	1,126	932	456	263	94	68	26	14,700
	1955–59	13,192	1,546	1,194	1,311	1,084	530	305	110	78	30	19,379
	1960–64	12,967	1,499	1,177	1,283	1,071	521	303	110	75	26	19,030
	1965–69	12,708	1,452	1,149	1,238	1,054	510	291	105	70	25	18,600
	1970–74	12,380	1,409	1,118	1,197	1,007	499	276	100	65	25	18,075
	Total	60,612	7,243	5,669	6,154	5,147	2,515	1,437	519	356	131	89,782
35–39	1950–54	9,625	1,406	1,179	1,439	1,119	532	319	95	55	34	15,802
	1955–59	14,318	1,621	1,370	1,673	1,290	604	366	105	63	38	21,447
	1960–64	13,967	1,580	1,327	1,629	1,253	590	346	102	60	35	20,888
	1965–69	13,470	1,541	1,285	1,575	1,205	570	340	94	58	35	20,171
	1970–74	12,736	1,487	1,240	1,526	1,134	541	318	85	52	33	19,151
	Total	64,116	7,635	6,401	7,841	6,000	2,837	1,689	480	287	174	97,458
40–44	1950–54	8,724	1,157	1,099	1,271	979	604	310	119	36	51	14,349
	1955–59	12,940	1,304	1,249	1,427	1,118	690	360	130	40	60	19,317
	1960–64	12,375	1,231	1,206	1,357	1,065	643	340	127	31	57	18,431
	1965–69	11,703	1,125	1,150	1,281	1,014	606	315	117	30	55	17,393
	1970–74	10,777	1,008	1,046	1,153	926	556	280	108	30	48	15,932
	Total	56,518	5,824	5,749	6,488	5,101	3,099	1,604	601	167	271	85,421
45–49	1950–54	7,427	988	935	1,154	894	389	259	77	64	30	12,215
	1955–59	10,359	1,127	1,046	1,303	983	446	291	90	75	35	15,754
	1960–64	9,738	1,075	964	1,242	918	417	269	90	75	28	14,813
	1965–69	8,972	987	867	1,138	847	368	248	85	74	16	13,599
	1970–74	7,821	876	751	1,000	717	295	211	70	55	6	11,799
	Total	44,317	5,052	4,562	5,836	4,358	1,913	1,277	410	342	113	68,179
≥50	1950–54	15,905	2,347	1,849	2,235	1,648	819	391	114	39	48	25,393
	1955–59	20,139	2,313	1,883	2,288	1,652	777	394	102	35	42	29,624
	1960–64	15,591	1,778	1,467	1,848	1,287	589	322	85	27	34	23,025
	1965–69	11,382	1,313	1,048	1,319	873	392	238	55	15	24	16,656
	1970–74	7,400	852	728	849	571	271	151	25	5	15	10,866
	Total	70,415	8,602	6,975	8,538	6,030	2,847	1,495	380	120	163	105,562
Total	1950–54	111,103	15,892	12,122	14,467	10,810	5,844	3,271	1,312	610	522	175,953
	1955–59	152,981	18,008	13,769	16,467	12,230	6,607	3,723	1,485	700	590	226,557
	1960–64	146,044	17,173	13,104	15,776	11,613	6,277	3,555	1,449	673	559	216,221
	1965–69	139,050	16,346	12,402	14,906	10,957	5,920	3,371	1,383	638	531	205,501
	1970–74	131,195	15,495	11,703	13,996	10,247	5,592	3,138	1,286	591	489	193,730
	Total	680,371	82,913	63,099	75,610	55,856	30,240	17,057	6,913	3,212	2,690	1,017,960